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Circadian disruption in women with breast cancer.

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CIRCADIAN DISRUPTION IN WOMEN WITH BREAST CANCER

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A Dissertation Approved on

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DEDICATION

This dissertation is dedicated to my parents, Steve Dedert and Brenda Kintz, who answered my questions when I was child and encouraged me to keep asking more.

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ABSTRACT

CIRCADIAN DISRUPTION IN WOMEN WITH BREAST CANCER

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Cancer patients show circadian disruption that increases as disease progresses. Disrupted endocrine and activity rhythms predict early metastatic cancer mortality. Effects of psychological versus biological factors on rhythms are unknown, as are potential links between endocrine and sleep disruption, and relevance of disruption in early stage cancer. This study sought to examine the associations of cancer-related intrusions and avoidant coping with circadian cortisol rhythms, assessed with saliva samples, and rest/activity rhythms, assessed with actigraphy. Participants were women who had been recently diagnosed with breast cancer, meaning participants provided data at similar points in the course of diagnosis and treatment of cancer.

Between diagnosis and surgical treatment, 45 women with breast cancer completed four days of data collection including daily reports on intrusions (IES intrusion scale) and avoidant coping (Brief COPE avoidant coping subscales), 12 saliva samples (waking, +30 minutes, 16:00 hours, bedtime), and actigraphy recordings. Mean intrusion and avoidant coping scores were calculated. Cortisol EIA assay results were examined for outliers and log-transformed prior to calculation of the diurnal slope. Actigraphy yielded the activity rhythm (autocorrelation coefficient), activity while in bed and out of bed (dichotomy index), and sleep variables. This study was unique in its opportunity to

explore circadian disruption through collection of multiple measures of circadian rhythmicity and daily reports of breast cancer-related intrusions and avoidant coping while patients adjusted to diagnosis and anticipated treatment.

Hierarchal regression analyses adjusted for relevant demographic and medical variables. Intrusions and avoidant coping were independently related to activity rhythm disruption (R2 change = .146 and .098, p = .008 and .034, respectively). Avoidant coping was associated with higher activity while in bed (R2 change = .168, p = .006). Circadian rhythm measures, diurnal cortisol slope and autocorrelation, were significantly associated in the predicted direction ($r = -.613$, $p < .001$). Higher autocorrelation was related to higher waking, and lower bedtime cortisol ($r = -.459$, $p = .003$). Breast cancer-related intrusions and avoidant coping may influence circadian rest/activity with possible implications for clinical intervention.

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INTRODUCTION

Breast cancer currently has the highest incidence of any cancer experienced by women. Estimates indicate approximately 213,000 women will be diagnosed with breast cancer in the United States in 2006 (National Cancer Institute [NCI], 2005). Breast cancer accounts for an estimated 30.7% of all newly diagnosed cancers in women in the United States (NCI, 2005). Breast cancer also accounts for 15.7% of cancer-related death in American women, trailing only lung cancer (NCI, 2005). While breast cancer mortality rates have declined in the United States in recent years, incidence rates have remained stable, and breast cancer is expected to continue to afflict many women. An estimated 12.67% of women born in the United States today are expected to develop breast cancer at some point, with an estimated 2.96% dying of breast cancer (NCI, 2006). An estimated $8.1 billion are spent annually on treatment of domestic breast cancer (NCI, 2005).

Breast Cancer Staging

At the time they are informed of a diagnosis of breast cancer, women may also receive information about their disease stage, a grouping of patients by the extent of tumor spread. Cancer that originates in the breast, as opposed to spreading from another part of the body, is referred to as primary breast cancer. Primary breast cancer can be staged between 0 and IV according to the staging system developed by the American Joint Committee on Cancer (2006). According to this system, staging is determined by the size of the tumor and involvement of lymph nodes in metastasis, the spread of cancer

from its primary site. Cancer that has spread from its primary site and invaded other sites in the body is termed metastatic.

Treatments

Women diagnosed with early stage breast cancer, typically less than stage III, are often given surgical treatment options that include total mastectomy, a removal of the entire breast, or partial mastectomy, removal of the cancerous portion of the breast as well as some of the healthy tissue around it. These surgeries are often accompanied by breast reconstruction surgery. Patients are also often given the option of breast-conserving surgery, called a lumpectomy, which removes the cancer and a minimal amount of tissue surrounding it, but leaves most of the breast intact. Existing research suggests that when breast-conserving surgery is paired with radiation that kills cancer cells, survival is similar to that of women receiving a mastectomy (NCI, 2004). In addition, a six-year follow-up study found no differences in psychological adjustment between women undergoing breast-conserving surgery and those receiving mastectomy (Omne-Ponten, Holmberg, & Sjoden,1994). Mastectomy is still chosen by some women to avoid undergoing radiation or reduce the chance of recurrence in the same breast (Molenaar, et al., 2001). Of women diagnosed with early stage breast cancer, an estimated 41% receive mastectomy, 37% receive breast-conserving surgery paired with radiation, and 19% receive breast-conserving surgery without radiation (National Institute of Health [NIH], 2005)

For patients whose primary breast cancer has spread to their lymph nodes, chemotherapy is generally recommended. Chemotherapy uses drugs to target and kill

rapidly-growing tumor cells. Chemotherapy drugs are taken orally, injected intravenously, or placed near the cancer site. An estimated 69% of patients with cancer metastasis to lymph nodes receive chemotherapy (NIH, 2005).

Some hormones, particularly estrogen and progesterone, are capable of stimulating the multiplication of cancer cells. Consequently, hormone therapies (e.g. tamoxifen, aromatase inhibitors) aim to block the activity of hormones that stimulate cancer cells. Hormone therapy offers potential benefits only for tumors with estrogen or progesterone receptors.

Symptoms Associated with Diagnosis

The course of breast cancer is frequently marked by manifestations of psychological distress including depression, anxiety, disrupted social and sexual functioning, self-image changes, fears of recurrence (Northouse, Templin, Mood, & Oberst, 1998; Rowland & Massie, 1998; Yurke, Farrar, & Anderson, 2000), as well as pain, hot flashes, weight gain, and vaginal discharge and dryness (Avis, Crawford, & Manuel, 2005). Quality of life studies support the notion that the period immediately following diagnosis, and including treatment, is the most troublesome for patients with breast cancer (Knobf, 2007). A recent review reported as much as 30% of patients develop an anxiety or depressive disorder within the first year after diagnosis (Edwards, Hailey, & Maxwell, 2004). Additionally, patients report more distress during the pre-treatment period than during the post-treatment period (Culver, Arena, Antoni, & Carver, 2002; Northouse, 1989). Patients also report elevated symptom distress related to insomnia, loss of concentration, and fatigue during the pre-treatment period (Cimprich,

1999). In candidates for surgical treatment, part of this distress could be due to the decision between mastectomy and breast-conserving surgery. Patients are generally interested in participating in this decision (Degner et al., 1997), but the acquisition of complex information and weighing of risks and benefits, in addition to adjusting to the diagnosis itself, is taxing for many patients. While distress is primarily evident prior to treatment, significant long-term distress has been noted in 18% of patients in a study of patients 20 years after diagnosis (Kornblith et al., 2003). In addition to the burden of distress experienced pre-treatment, this distress has been associated with post-treatment pain, nausea, fatigue, and discomfort in at least one sample of patients with breast cancer (Montgomery, & Bovbjerg, 2004).

Distress, Psychiatric Morbidity, and Quality of Life

While many studies have documented the difficulty of psychological adjustment to breast cancer, the prevalence of these difficulties are unclear due to inconsistent findings. For example, prevalence reports regarding depression in women with breast cancer have ranged from 1.5% to 50% (Rowland & Massie, 1998). Disparities in reports of psychological disorders in these patients have numerous explanations. Because a number of instruments for measuring depressive symptoms are available, depression research can be used as an example of the effect of methodology on estimates of prevalence rates in patients with breast cancer. The Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition (APA, 1994) specifies criteria for a Depressive Episode that have substantial overlap with the consequences of illness and medical treatments such as chemotherapy. Anhedonia, decreased appetite, sleep disturbance,

reduced psychomotor activity, and fatigue might all be secondary to cancer and its treatment, confounding even a skilled assessment.

Differences between studies in the methods of addressing this issue likely account for some of the variance in reports of depressive symptomatology (Trask, 2004). For example, some studies have measured and used all symptoms of depression regardless of whether they are caused by a general medical condition (Rifkin et al., 1985). This approach maximizes sensitivity for detecting symptoms of depression but decreases specificity. A likely result is that depression estimates using this method are inflated. Conversely, fatigue and appetite/weight changes, two symptoms often confounded with medical conditions, have been eliminated from assessments of depression in samples of patients with a medical condition (Bukberg, Penman, & Holland, 1984). This method maximizes specificity at the expense of sensitivity and likely underestimates symptoms of depression. Alternatively, a symptom of depression has sometimes been counted only if it is clearly not attributable to a general medical condition as determined by the interviewer or investigator (Rodin, Craven, & Littlefield, 1991). To the extent that the etiology can be determined, this method is useful, but determinations regarding symptom etiology can be challenging, even for skilled interviewers (Trask, 2004). Some researchers have addressed this issue by distinguishing between somatically and cognitively focused symptoms such as helplessness, hopelessness, indecisiveness, or pessimism (Endicott, 1984). This method matches the assessment to the specific medical population, but there is no consensus regarding which symptoms are most appropriate to use (Trask, 2004) and how well the resulting depression estimates compare to estimates using formal criteria for a depressive disorder.

Confusion regarding symptom etiology is not the only potential confound contributing to variability in estimates of psychiatric morbidity in patients with breast cancer. Studies use both interview and written self-report measures to assess psychological disorders and symptomatology. While a diagnostic interview is preferable for establishing the presence of a psychological disorder, self-report questionnaires are frequently more feasible. Studies using a self-report questionnaire sometimes employ a cutoff score to indicate which patients are likely suffering from clinically significant depression, but these measures tend to yield a high number of false positive diagnoses (Lynch, 1995).

Variability in the assessment of psychological disorders can also be derived from differences in who assesses the patient. Routine screening for depression often does not exist, and research suggests a minority of patients are likely to report symptoms of depression to nonpsychiatric hospital staff (Koller et al., 1996; Passik et al., 1998). As a result, archival studies of depressive symptoms may underestimate the prevalence of depression in patients with breast cancer.

Finally, the symptomatology of many psychological disorders, especially depression and anxiety disorders, may worsen and remit throughout the diagnostic and treatment processes (Trask, 2004), so the time of assessment could also contribute to variability in prevalence estimates. Existing research suggests the first 13 months after diagnosis produce the most distress, with decreasing levels thereafter (Helgeson, Snyder, & Seltman, 2004). Long-term studies suggest that after this period, psychiatric disorder prevalence rates of women that were diagnosed with breast cancer approach those of the general population (Coyne, Benazon, Gaba, Calzone, & Weber, 2000). While the rates of

psychiatric disorders for women that are more than one year post-diagnosis may be only mildly elevated relative to the general population, subclinical distress and impairment in excess of average rates are evident (Rowland & Massie, 1998). These considerations are in addition to those of age, race, subculture, and differences between self-report measures that typically contribute to variability.

Elevated levels of depressive and anxious symptomatology have consistently been reported by patients with newly diagnosed breast cancer on self-report measures (Cimprich, 1999; Compas & Luecken, 2002). For example, a large survey reported that 33% of patients with breast cancer suffered from significant distress (Zabora, Brinzenhofeszoc, Curbow, Hooker, & Piantodosi, 2001). However, studies investigating the prevalence of psychological disorders in these patients have yielded conflicting results. In a recent study using a semi-structured diagnostic interview that followed patients longitudinally, at least borderline criteria for a depression or anxiety disorder as listed in the Diagnostic and Statistical Manual of Mental Disorders – Third Edition (DSM-III; APA, 1987) were endorsed by 33% of patients at diagnosis, 24% at three months after diagnosis, and 15% one year after diagnosis (Burgess et al., 2005). However, another study of newly diagnosed patients using a semi-structured interview found the prevalence of psychiatric disorders to be 18%, similar to that of community epidemiological surveys (Dausch et al., 2004). It should be noted that the latter study was comprised of psychosocial treatment-seeking individuals and excluded patients with a history of a psychotic psychiatric disorder or current metastatic disease. These differences could account for the discrepancy between the two studies.

Studies of psychological well-being, specifically, have been supplemented by studies of the broader quality of life concept. The term quality of life is multidimensional (Aaronson, Bullinger, & Ahmedzai, 1988; Cella, 1994), and its measurement typically assesses social, emotional, physical, and functional well-being and may also include spiritual, financial, and sexual well-being (McQuellon, Kimmick, & Hurt, 1997). Several studies have noted improved quality of life within the first year after completing treatment (Land et al., 2004; Stanton, Danoff-Burg, & Huggins, 2002). Still, the research literature contains several reports of elevated symptomatology years after diagnosis or treatment, including increased fatigue (Bower et al., 2000).

The abundance of methodological issues complicating assessment of psychiatric morbidity and quality of life in patients with breast cancer explain the strikingly disparate estimates sometimes found in the literature. In evaluating these estimates, the appropriateness of existing criteria, assessment methods and interviewers to the patient population should be considered. The patient's place in the course of diagnosis and treatment should also be considered.

Clearly, methodological differences contribute to significant variability in psychiatric morbidity and quality of life in patients with breast cancer, but some patterns have emerged. Generally, the available literature suggests that women who are diagnosed with breast cancer experience increased distress and impaired quality of life for at least the first year after diagnosis. However, it appears that despite the continued presence of some residual symptoms resulting from breast cancer diagnosis and treatment, long-term psychological morbidity prevalence rates and quality of life improve following successful treatment of breast cancer.

Intrusions

Intrusions are defined as "unwanted thoughts and images related to the stressor" (Antoni, Wimberly, et al., 2006, p. 1793). Intrusions have also been defined as "intrusively experienced ideas, images, feelings, or bad dreams" (Zilberg, Weiss, & Horowitz, 1982, p. 407). They can be elicited by environmental stimuli associated with the stressor or internal stimuli such as thoughts associated with the stressor.

Intrusions related to a stressor are, in addition to being unwanted, typically distressing to the individual. As reactions to a stressor, intrusions are categorized as a type of psychological distress (Horowitz, & Wilner, 1979). As a type of distress, intrusions compromise emotional well-being, a component of the patient's quality of life. Surprisingly, intrusions do not always correlate highly with generalized distress. Cancer-related intrusions and distress were only mildly associated with each other ($r = .34$) in a study of patients that had been recently diagnosed with cancer at several different sites, with the most prevalent being breast cancer (37%; Epping-Jordan, Compas, & Howell, 1994). Patients in this study varied with respect to cancer site, with breast cancer being the most common diagnosis. Different results were found in a study of people who were registered as outpatients at an oncology department and had immigrated to Israel from Russia between the years of 1989 and 1992. These patients also had varied cancer sites, with breast cancer being the most common (44%). Cancer-related intrusions and distress were more strongly correlated ($r = .64$) among the women in this study (Baider, Kaufman, Ever Hadani, & Kaplan De-Nour, 1996), though this could be influenced by the stress of immigration.

Although it was initially developed to study individuals during bereavement, the Impact of Event Scale (IES) has frequently been employed to measure reactions to trauma (Sundin & Horowitz, 2002). The IES measures two aspects of trauma: intrusions and avoidance. Diagnostic criteria for Posttraumatic Stress Disorder (PTSD) include re-experiencing of the traumatic event and avoidance of event-specific cues as symptoms of the disorder. The re-experiencing criterion includes intrusions, as well as other manifestations such as dreams of the event or feeling as though one is reliving the event. A diagnosis of PTSD requires that the reaction be in response to a traumatic event, so intrusions are consistent with psychiatric morbidity that is tied to the original stressor. As a result, intrusions are an indicator of continued distress or impairment related to a stressful event. However, as persisting cues to think about a stressor, intrusions can prompt continuing stress for the individual. Consistent with this idea, intrusions have been conceptualized as efforts to process new information (Park & Folkman, 1997), suggesting that processing is necessary to resolve these thoughts. Ehlers and Steil (1995) proposed a model of intrusive memories and thoughts asserting that when intrusions are assigned a negative meaning, the individual is more likely to engage in avoidance, which increases the frequency of intrusions. This model suggests that intrusions will recur, especially when an individual engages in avoidant coping.

Intrusions related to breast cancer are prevalent, with 35% of patients endorsing "repeated, disturbing memories of cancer treatment or your experience with cancer" in one study of women who were primarily more than one year post-diagnosis (Jacobsen et al., 1998). Scores of 20 or more on the Intrusions subscale of the Impact of Event Scale (IES) are considered indications of a stress response syndrome (Bleiker, Pouwer, van der

Ploeg, Leer, & Ader, 2000; Horowitz, & Wilner, 1979). High levels of cancer-related intrusions associated with a score of 20 or more on the IES intrusions subscale have been observed in 16% of patients two months after surgery, while scores in the moderate range of 9-19 in IES intrusions were observed in 30% of the same patients two months after surgery. Of the patients endorsing high levels of intrusions, 60% continued to report high intrusions 21 months after surgery, suggesting temporally stable distress resulting from the diagnosis (Bleiker et al., 2000). Intrusions are likely to be associated with other psychological morbidity and have been related to anxiety and depression at the time of diagnosis and 3 months post-diagnosis in a sample of patients with cancer at varying sites (Epping-Jordan et al., 1994) and at 6 months post-diagnosis in a sample consisting entirely of patients with breast cancer (Primo et al., 2000).

The relationship between intrusions and endocrine alterations in people who have endured a traumatic event (Yehuda, 2002), the high prevalence of intrusions in patients with breast cancer, and the prominence of PTSD among mental disorders observed in women recently diagnosed with breast cancer (Dausch et al., 2004) suggest that cancer-related intrusions may be a more sensitive index of a patient's response to breast cancer than are general measures of stress or distress. Consequently, intrusions present an intriguing psychological variable with respect to physical health. Research on this relationship is not extensive, but cancer-related distress, as measured by the sum of all intrusion and avoidance items on the IES (Horowitz, & Wilner, 1979), has been related to several indicators of immunosuppression in women who had received surgical treatment for breast cancer in the past four months and had not yet begun adjuvant treatment. Overall cancer-specific distress was associated with impaired ability of natural killer

(NK) cells to attack target cells, decreased proliferative response to T-cell receptors, and decreased response to mitogens (Andersen et al., 1998).

Because cancer-related intrusions are a significant and common problem for patients with breast cancer, a cognitive-behavioral intervention has been designed to target these intrusions and has demonstrated evidence of efficacy in women receiving surgical treatment for breast cancer (Antoni, Wimberly, et al., 2006). A supportive-expressive therapy trial targeted and reduced overall traumatic stress symptoms in women with metastatic breast cancer (Classen et al., 2001). In addition, patients with high overall cancer-specific distress, which includes an intrusion subscale, have realized greater mood improvement from psychological intervention (Andersen et al., 2004).

Diagnosis of Cancer as a Trauma

A breast cancer diagnosis has been shown to produce symptoms consistent with those used to determine a diagnosis of Posttraumatic Stress Disorder (PTSD) diagnosis in some patients (Andrykowski, Cordova, Studts, & Miller, 1998). These findings are mirrored by an inclusion of life-threatening illness among the Criterion A events that can potentially precipitate PTSD in the DSM-IV (APA, 1994). Symptoms consistent with PTSD must be present for at least one month to meet criteria for a diagnosis of PTSD. Prior to that time, trauma-related symptoms may meet criteria for Acute Stress Disorder, though more dissociative symptoms are required for diagnosis of Acute Stress Disorder, as opposed to PTSD (APA, 1994). One study of patients in remission and six or more months removed from treatment found that 6% of patients met criteria for PTSD (Andrykowski et al., 1998). Another study assessed women 3-6 weeks after diagnosis and

found that while only 18% of the sample met criteria for a mood, anxiety, or adjustment disorder, 8% of these diagnoses were for PTSD or Acute Stress Disorder (Dausch et al., 2004). In women responding to self-report questionnaires 6-60 months after completing treatment for early stage breast cancer, 5-10% responded in a way suggestive of a diagnosis of PTSD (Cordova et al., 1995). A study of women who were 4-12 months post-treatment for early stage breast cancer found that 3% of women met strict current or past criteria for PTSD based on the cancer diagnosis as the traumatic event, but subsyndromal PTSD symptoms were commonly reported. Cancer-related intrusive thoughts were reported by 36% of these patients, 48% met the re-experiencing criterion, and 36% endorsed three or more symptoms of PTSD (Green et al., 1998).

At first glance, the disparity between intrusions and PTSD diagnoses may be surprising because intrusions are part of the diagnosis of PTSD. Some of this disparity could be attributed to methodological differences between measurement of intrusions, which are often assessed using self-report measures, and PTSD diagnoses assessed by interview. Further, although it is clear that intrusions are present to a significant degree in women diagnosed with breast cancer (Butler, Koopman, Classen, & Spiegel, 1999), PTSD is only an appropriate diagnostic category for a subset of these women. PTSD criteria specify that intrusions consist of recollections, dreams, or re-experiencing of the traumatic event, but intrusive thoughts reported by women with breast cancer may consist of future-oriented worry about treatment, cancer progression, recurrence or death that are not truly intrusions and does not fit PTSD criteria (Green et al., 1998). Existing research on traumatic reactions is consistent with findings regarding other psychiatric diagnoses in that the primary elevations in the prevalence of PTSD occur shortly after diagnosis.

In addition to being linked with general distress, intrusions may influence physiology. Intrusions have demonstrated relationships with impaired immune responses (Andersen et al., 1998). Intrusions have also been linked with immunosuppression in students anticipating an examination (Workman & La Via, 1987). In addition, in men undergoing testing for HIV, intrusions were correlated with increased cortisol at 1 week, 3 weeks, and 5 weeks after being informed of test results (Antoni et al., 1990).

HPA axis description

A model of HPA axis activation is presented in Figure 1 below. Human physiological responses to stress appraisals have consistently demonstrated activation of a specific pathway beginning with the hypothalamus (corresponding to arrow A in the model depicted in Figure 1) (McEwen, 1998), which secretes corticotropin-releasing hormone (CRH) (arrow B). CRH triggers the pituitary gland to secrete adrenocorticotropic hormone (ACTH) (arrow C), causing the adrenal cortex to secrete cortisol (arrow D). Cortisol produces metabolic changes, mobilizing energy by promoting the conversion of protein and lipids to usable carbohydrates, providing the organism with the energy resources to confront a stressor (McEwen, 2004) and ideally alter characteristics of the stressor to make it less stressful. The neurohormonal cascade resulting in cortisol secretion is a physiological negative feedback loop, with cortisol actively inhibiting subsequent activation of this system (arrow E). As a result of heightened secretion under stress, cortisol presents one means of assessing the effects of psychosocial stress on physiological functioning. The neurohormonal pathway described above is collectively referred to as the Hypothalamic-Pituitary-Adrenal (HPA) axis.

Figure 1. An illustration of the Hypothalamic-Pituitary-Adrenal (HPA) axis.

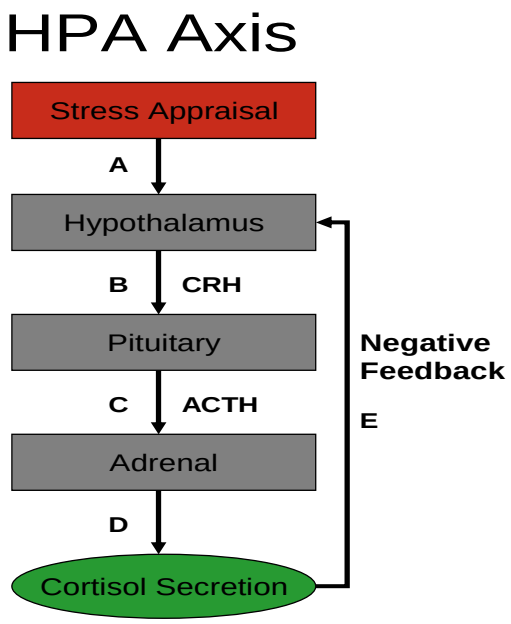


Figure 1 illustrates stress-related activation of the hypothalamic-pituitary-adrenal (HPA) axis. The arrows represent different phases of the HPA activation process A) Appraisals of stress stimulate the hypothalamus; B) The hypothalamus secretes corticotropin-releasing hormone (CRH); C) CRH stimulates the pituitary gland to secrete adrenocorticotropic hormone (ACTH); D) ACTH stimulates the adrenal gland to secrete cortisol; and E) Cortisol inhibits subsequent activation of the HPA axis.

Changes in HPA axis reactivity have been reported in association with chronic stressors such as anxiety (McEwen, 1998), early childhood trauma (Heim, Ehlert, & Hellhammer, 2000), socioeconomic status (Brandtstadter, Baltes-Gotz, Kirschbaum, & Hellhammer, 1991), and depression (Heim et al., 2002). HPA axis reactivity has also been evident in response to short-term distress (Seeman, Burton, Rowe, Horwitz, & McEwen, 1997), including completion of a mammogram (Porter et al., 2003) and laboratory stressors including a public speaking task (Kirschbaum, Wust, & Hellhammer, 1992) and a distress-inducing vigilance task in healthy adults (Lundberg & Frankhaeuser,

1980). Taken together, these studies support the notion that distress is associated with increased cortisol production and argue for the usefulness of cortisol as a physiological measure of stress reactivity.

The physiological responses to acute stressors aimed at short-term adaptation have been termed allostasis, meaning "the ability to achieve stability through change" (McEwen, 1998, p. 171). Allostasis incorporates responses from several systems in the body, including the HPA axis, the autonomic nervous system, and the cardiovascular, metabolic, and immune systems. Stress-related activation of the HPA axis as part of allostasis results in cortisol secretion and the associated mobilization of energy through the availability of carbohydrates (McEwen, 2004). Once a stressor is removed, allostatic responses aimed at addressing acute stressors are generally inactivated, returning HPA axis activity to its baseline state.

Although the adaptation promoted by allostasis is critical, accommodations to stress can exact a toll on the body over time due to chronic underactivation or overactivation of bodily systems influenced by allostasis. The wear and tear on the body associated with repeated stress or insufficient deactivation of allostatic responses has been termed allostatic load (McEwen & Stellar, 1993). Allostatic load can develop due to exposure to frequent and varied stressors, failure to adapt to repeated stressors of the same type, or failure of stress responsive systems to return to baseline following the removal of the stressor (McEwen, 1998). In these instances, chronic overexposure to stress hormones such as cortisol can bring about pathophysiologic consequences. For example, chronic overactivation of the HPA axis can lead to disruption of circadian physiological rhythms, which may be linked with suppressed immune function, sleep disruption, and increased

cancer incidence and progression (Sephton & Spiegel, 2003). Continued overactivation of the HPA axis has also been associated with varying conditions including memory impairment, hypertension, osteoporosis, insulin resistance, and cardiovascular disease (Chrousos & Gold, 1998). Among the effects of HPA axis activation on the body are alterations of the immune system. End-products of the HPA axis such as cortisol inhibit cytotoxicity, the ability of some types of immune cells to destroy target cells. Stress responses can also reduce availability in the body of immune cells such as lymphocytes and affect secretion of cytokines such as interleukin-2 (essential to fighting infection) and interferon-γ, which has anti-tumor properties (Elenkov & Chrousos, 1999).

Just as overexposure to stress hormones can be problematic, hyporesponsivity of the HPA axis can also lead to allostatic load. The immune system component of allostasis is typically regulated by glucocorticoids such as cortisol. When cortisol levels are insufficient for inactivation of the immune response following removal of the stressor, the organism is at increased risk of autoimmune or inflammatory disturbances associated with a sustained exposure to inflammatory cytokines (McEwen, 1998).

Transactional Model

The transactional model of stress, coping, and adaptation originally proposed by Lazarus and Folkman (1984) asserts that the person and his or her environment are in a "dynamic, mutually reciprocal, bidirectional relationship" (p. 293). Stress is defined in this model as "a relationship between the person and the environment that is appraised by the person as taxing or exceeding his or her resources and endangering his or her well-

being" (Lazarus & Folkman, 1984, p. 21). Figure 2 illustrates the transactional model of stress and coping.

In this model, an individual engages in a primary appraisal evaluating whether, and to what extent, an encounter is challenging, threatening or harmful (i.e. stress). If an encounter is deemed stressful, the person then engages in secondary appraisal, an evaluation of the availability of coping options, the effectiveness of available coping options, and the person's ability to enact these coping options. Secondary appraisals and primary appraisals work together to determine the precise degree of stress perceived by the individual. Plentiful availability of easily enacted coping strategies that are expected to be effective in reducing or ameliorating the stressor are likely to reduce a person's perception that the encounter is stressful. Conversely, the absence of cognitively available coping options, ineffectiveness of available coping options, or a person's doubt in their ability to successfully enact coping responses may increase stress appraisals. It should be noted that stress appraisals may not be significantly altered by secondary appraisals. For example, this may be true for encounters in which a person appraises the outcome stakes to be particularly high.

Following the appraisal process, coping efforts are employed. The outcome of the coping process continues to work together with primary and secondary appraisals to shape a person's experience of an encounter as stressful. These relationships are complex and likely to vary considerably between individuals, but discussion of ways in which primary and secondary appraisals and coping could work together may illustrate their conceptual relationships. For instance, if coping successfully reduces the threat or harm produced by the stressor or ameliorates the effects of the stressor on the person's

emotional well-being, the encounter may be appraised as being less stressful. Unsuccessful coping, in contrast, may modify secondary appraisals, lessening the person's perceptions that effective coping responses are available. This may influence primary appraisals, strengthening the person's conviction that an encounter is threatening or harmful.

Figure 2. The transactional model of stress and coping

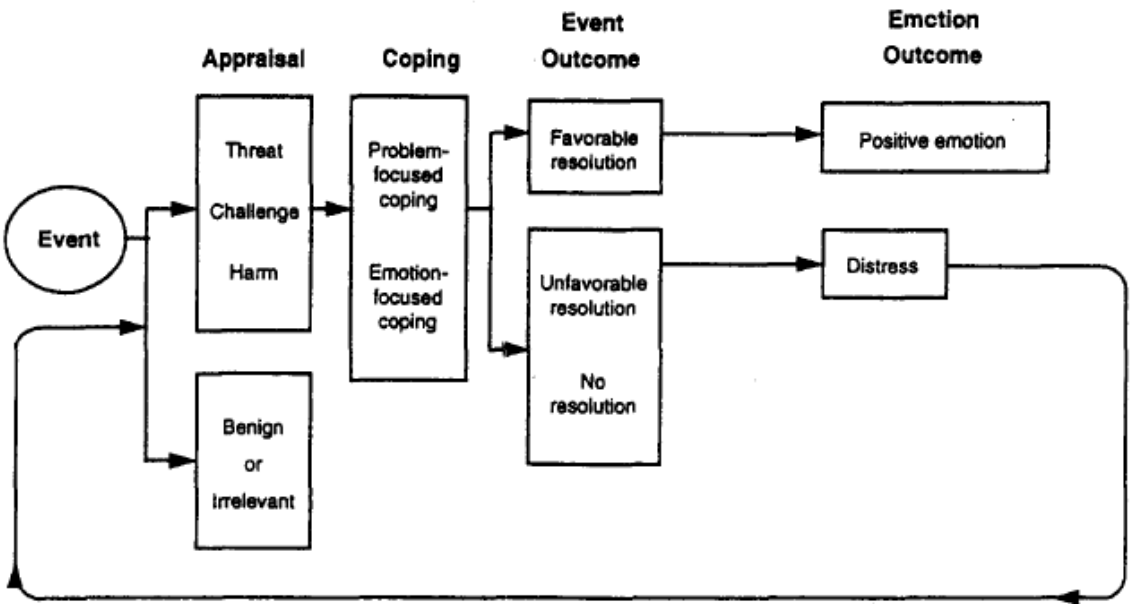


Figure 2 depicts the transactional model of stress, coping, and adaptation. When an event occurs, appraisal determines whether the event is threatening, challenging, or harmful. In addition, Coping efforts are consciously employed, and if the event is not favorably resolved, distress results. Model adapted from: Folkman, S. (1997). Positive psychological states and coping with severe stress. *Social Science & Medicine, 45*(8), 1207-1221.

According to the transactional model, characteristics of the person, stressor, and situation influence how people appraise and cope with a potential stressor (p.147) (Lazarus & Folkman, 1984). The implications of the dynamic features of the transactional model are that it is desirable to specify relevant characteristics of a stressful encounter to better understand the process involving stress and coping.

Coping

Coping is most commonly defined as "constantly changing cognitive and behavioral efforts to manage specific external and/or internal demands that are appraised as taxing or exceeding the resources of the person" (Lazarus, & Folkman, 1984, p. 141). While stressors are often associated with physiological arousal, the relationship between stressful events and an individual's physiology and physical health is complex, and the relationship is likely modified by coping strategies (Taylor, Repetti, & Seeman, 1997). Research on physiological adaptation to stressors has noted that exposure to stressors can lead to positive physiological changes and that these physiological changes are influenced by the psychological responses of the individual including appraisals and perceptions of control (Epel & McEwen 1998). As a result, the way in which coping influences physiological adaptation to stressors has been investigated. Researchers have used observational studies as one way to investigate the relationships of coping with distress, physiological variables, and health outcomes, as reviewed below.

Active coping

Coping strategies have been categorized as either active or avoidant and outcomes for the two types of coping strategies have been contrasted. Active coping is defined as "the process of taking active steps to try to remove or circumvent the stressor or to ameliorate its effects" (Carver, Scheier, & Weintraub, 1989, p. 268). Evidence indicates that an active coping style, as opposed to an avoidant coping style, has generally been associated with enhanced psychological adjustment (Luecken & Compas, 2002). Active

coping has been found to predict better long-term psychological adjustment in women with breast cancer (Epping-Jordan et al., 1999; Stanton, Danoff-Burg, & Huggins, 2002). In addition, in women undergoing breast biopsy, patients who utilized coping efforts characterized by actively confronting their illness reported less psychiatric morbidity (Chen et al., 1996). Several studies have documented a possible relationship between emotional expression, rather than inhibition of emotional responses, and slowed progression of cancer (Gross, 1989). Although opinions on the effects of active coping on survival differ (Faller, 2001; Petticrew, Bell, & Hunter, 2002), interview ratings of active coping in patients with lung cancer have been related to increased survival (Faller, 2001). Strategies for addressing or ameliorating the stressor, or problem-focuses coping strategies, have also been studied in patients with breast cancer. Information seeking shortly after being informed of a breast cancer diagnosis has predicted subsequent improved physical quality of life six month post-diagnosis (Ransom, Jacobsen, Schmidt, & Andrykowski, 2005). The mechanism of the effects of problem-solving coping on physical health outcomes has not been established, but constructs such as information seeking incorporate openness to different treatments (Ray et al., 1993). Improved health behavior such as adherence to medical regimen, increased exercise, improved nutrition, and decreased smoking are also possible consequences of problem-focused coping that could improve physical health outcomes (Ransom et al., 2005).

Additionally, emotionally expressive coping, defined as the utilization of emotional outlets as a means of intentionally focusing on the individual's reaction to the stressor, has predicted better quality of life, enhanced physical health, decreased psychological distress and fewer medical appointments in HIV-infected men (Mulder, Antoni,

Duivenvoorden, Kauffman, & Goodkin, 1995).

Watson et al. (1988) developed the Mental Adjustment to Cancer (MAC) scale to measure a person's mental adjustment to cancer, but it has since come to be used as a measure of coping. Nevertheless, examination of the items on the MAC reveal that the original conceptualization is likely more accurate. Although some items seem to assess coping efforts or resources, most items assess psychological reactions more consistent with distress, specifically depression and anxiety. Among the responses assessed is hopelessness/helplessness, a psychological reaction characteristic of depression that incorporates low expectation for future paired with a sense of inability to influence the future. This subscale is assessed with questions such as "I think it is the end of the world" and "I feel like giving up" (Watson et al., 1988). The disengagement that typically accompanies feelings of helplessness is characteristic of avoidant coping. The MAC also measured anxious preoccupation, which seemed to be a composite of anxiety and generalized distress. This subscale included questions such as "I suffer great anxiety about it" and "It is a devastating feeling" (Watson et al., 1994). Fatalism, another subscale of the MAC, seemed to target acceptance with limited hope for the future and used items such as "I've had a good life; what's left is a bonus" and "I count my blessings" (Watson et al., 1994). Finally, the MAC assessed fighting spirit, a construct that is the polar opposite to hopelessness/helplessness and consists of "regarding cancer as a challenge and adopting a positive attitude" (Greer, 2000, p. 847) and was measured using items like "I am very optimistic" and "I am determined to beat this disease" (Watson et al., 1994).

Some inconsistencies exist regarding the relationship between cancer stage and coping strategies employed. Patients do not restrict themselves to one type of coping strategy. Patients may employ multiple strategies over time, and the coping strategy employed could vary depending on the stage of the disease. A change from one strategy to another may be in response to a perception that initial strategies have been unsuccessful. The use of both active and avoidant coping concurrently may be adaptive for individuals faced with different types of stressors. Some evidence suggests that active coping strategies are used more often by women with early stage breast cancer (Schnoll, Harlow, Stolbach, & Brandt, 1998) and advanced stage has been linked with increased use of hopelessness/helplessness, anxious preoccupation, and fatalism (Schnoll et al., 1998). Studies have observed associations between advanced stage and both increased use of avoidant coping (Sandgren & McCaul, 2007) and decreased use of avoidant coping (Reynolds et al., 2000). Earlier stage has been associated with an elevated "fighting spirit" orientation to the disease (Lilja, 2003; Schnoll et al., 1998) and more problem-focused coping strategies (Cohen, 2002).

Avoidant coping

Horowitz and Wilner (1979, p. 210) characterized avoidance as involving "ideational constriction, denial of meanings and consequences of the event, blunted sensation, behavioral inhibition or counter-phobic activity, and awareness of emotional numbness." Avoidant coping is defined here as reducing one's cognitive and behavioral efforts to deal with the stressor (Carver, Scheier, & Weintraub, 1989). Consistent with its

definition, avoidant coping has generally been associated with findings opposite to those of active coping (Stowell, Kiecolt-Glaser, & Glaser, 2001).

Some evidence suggests a positive influence of avoidant coping, as one study found that women awaiting mastectomy who were judged by interviewers to be using denial coping strategies also report lower mood disturbance and state anxiety (Watson, Greer, Blake, & Shrapnell, 1984), but other research has generally observed a robust negative relationship between avoidant coping and psychological adjustment (Luecken & Compas, 2002; McCaul et al., 1999; Montgomery et al., 2003; Shapiro et al., 1997; Stanton & Snider, 1993; Wade, Nehmy, & Koczwara, 2005; Watson et al., 1991). Avoidant coping at the time of diagnosis has been shown to be predictive of increased distress as long as three years post-diagnosis (Hack & Degner, 2004). In breast cancer patients, avoidant coping has been associated with increased distress in women with early stage breast cancer (Carver et al., 1993) and increased fear of recurrence one year after diagnosis (Stanton, Danoff-Burg, & Huggins, 2002). An association between increased distress and avoidant coping in cross-sectional studies may seem counterintuitive, or at least paradoxical, given the definition of avoidant coping as a collection of consciousness lowering processes. It might be expected that avoidant coping would, by definition, be associated with reduced self-reported short-term distress. To explain these findings, it is necessary to draw on the distinction made by the transactional model of stress between coping functions and coping outcomes. This means that a person may engage in avoidant coping functionally without achieving or experiencing that outcome (Lazarus & Folkman, 1984).

In addition to effects on distress, avoidant coping has been researched as it relates to physical and physiological outcomes. This research has included repression, a concept that is similar to avoidant coping. Repression has been conceptualized as "a class of consciousness-lowering processes" (Erdelyi, 2006), and this process is consistent with reduction of efforts to deal with a stressor characteristic of avoidant coping (Brown et al., 1996). An association of repression with increased basal cortisol levels has been observed in college undergraduates (Brown et al., 1996). In a study of metastatic breast cancer patients, repression was directly associated with a flatter diurnal cortisol slope (Giese-Davis, Sephton, Abercrombie, Duran, & Spiegel, 2004), a variable previously found to be predictive of survival in the same sample (Sephton, Sapolsky, Kraemer, & Spiegel, 2000). An association has also been noted between repression and cancer progression in patients with breast cancer (Jensen, 1987).

In addition to the literature on the physiological effects of coping efforts on patients with breast cancer, there is evidence of significant relationships in other populations. Avoidant behavior marked by low exploration of novel environments and situations was related to elevated morning cortisol levels in children (Kagan, Reznick, & Snidman, 1988). Reaction formation, behaving a way opposite to something the individual wishes to avoid, has been conceptualized as an avoidant response (Prins & Beaudet, 1980) and has been associated with increased cortisol in non-swimming military recruits taking a swimming test (Vaernes, Ursin, Darragh, & Lambe, 1982). Rhesus monkeys that are slow to explore novel environments have been noted to have increased cortisol levels in response to separation from the mother (Suomi, 1987). This finding supports the notion of a contrast between active and avoidant coping and suggests that

avoidant coping is associated with poorer psychological and physical adaptation. It is noteworthy that harm avoidance, as a personality trait, has been linked with diminished ambulatory measured motor activity throughout the day. Personality traits differ from coping processes, but people high in Harm Avoidance have been described as having learned to "inhibit behavior to avoid punishment, novelty, and nonreward" (Volkers et al., 2002). This conceptualization suggests that individuals high in Harm Avoidance are likely to exhibit avoidance behavior as a means of coping with stressors.

Coping has also been a significant variable in a number of studies of immunity, suggesting that a person's response to a stressor can influence the physiological impact of stressors and the resulting distress. In HIV-positive men, active coping has been positively associated with improved immunity marked by natural killer cell cytotoxicity (Goodkin, Blaney, et al., 1992), lymphocyte proliferative response (Goodkin et al., 1996), leukocyte proliferative response, and slower clinical progression (Mulder, Antoni, Duivenvoorden, Kauffman, & Goodkin, 1995). Conversely, avoidant coping has been associated with poorer immune function in HIV patients (Goodkin, Fuchs, Feaster, Leeka, & Rishel, 1992) and reduced effectiveness of NK cells in patients with malignant melanoma (Fawzy et al., 1990). Similarly, in a sample of patients with various cancer sites, avoidance predicted disease status one year later (Epping-Jordan et al., 1994).

Existing literature on the HPA axis also suggests the distress associated with medical problems is related to greater physiological disturbance when people utilize avoidant coping. Research on avoidant coping and the HPA axis has noted increased cortisol output following arthroscopic knee surgery (Rosenberger, Ickovics, Epel, D'Entremont, & Jokl, 2004) and suppression of immune function in partners of patients

receiving bone marrow transplants (Futterman, Wellisch, Zighelboim, Luna-Raines, & Weiner, 1996). In addition to naturalistic studies of the HPA axis, the induction of stress in a laboratory setting has proven to be a useful tool. The most common lab stressor used is the Trier Social Stress Test, a task in which participants are asked to give a videotaped mock job interview speech before a panel of judges for five minutes. After the speech is completed, participants are then asked to serially subtract 13 from an initial value of 1,022 for 5 minutes (Young, Lopez, Murphy-Weinberg, Watson, & Akil, 2000). This task induces a mild to moderate increase in psychosocial stress and cortisol in most individuals (Kirschbaum, Pirke, & Hellhammer, 1993). As a result, this task can be used to investigate the responsiveness of the HPA axis to a psychosocial stressor.

The relationship between coping and physiological variables could be complex and may involve an interaction between stress, coping, and distress. Conceptualized within the framework of the transactional model of stress and coping, the effect of a stressor on outcomes may be influenced by coping. This relationship may be such that stress is associated with undesirable outcomes only when maladaptive coping is high, or adaptive coping is low. For example, there is variability in the ways in which individuals respond to the Trier Social Stress Test (Young et al., 2000), suggesting a possible influence of coping on the relationship between the stress induced in the laboratory and the individual's physiological response. Avoidant coping has been researched in people with schizophrenia using the Trier Social Stress Test. Results from this study suggested a blunted HPA axis response to the task in people reporting more avoidant coping (Jansen, Wied, & Kahn, 2000). Similarly, an investigation of this relationship in caregivers of family member with dementia noted that the interaction of perceived stress and avoidant

coping was generally, though not always, related to poorer leukocyte proliferative response to mitogens (Stowell et al., 2001).

Avoidant coping may influence the effect of stress or distress, specifically intrusions, on physiological outcomes as discussed in the previous paragraph. Avoidant coping may also directly influence physical or physiological outcomes, independently of the level of stress or intrusions present. The former relationship is one in which research asks "under which conditions does avoidant coping influence physiology?", while the latter relationship asks whether a simple influence of avoidant coping on physiology exists. The majority of the studies reviewed above have investigated and reported direct effects of avoidant coping on outcomes, with promising results. Consequently, direct effects of avoidant coping on physiology are of interest. Still, research on direct effects of avoidant coping may benefit from extension to the former question of identifying conditions under which a given coping strategy is helpful or harmful.

Based on the existing literature reviewed above, avoidant coping strategies appear to be an important component of response to breast cancer diagnosis and treatment with potential negative effects on psychological adjustment, activity levels, immunity, and cancer progression. Additionally, avoidant coping may be associated with increased cortisol output in response to acute stressors and disrupted circadian cortisol profiles.

Self-Distraction

The avoidant coping category subsumes several more specific coping efforts. One of these subtypes of avoidant coping, self-distraction, has also been referred to as mental disengagement (Carver et al., 1989). This coping effort includes activities to reduce

awareness of goals with which the stressor interferes (Carver et al., 1989) and typically takes the form of engaging in thoughts or activities that absorb the person's attention, successfully distracting from thoughts about the stressor. Previous research on this self-distraction suggests this construct is correlated with decreased optimism and perceived control, as well as increased anxiety (Carver et al., 1989). In women with gynecological cancer, pre-operative self-distraction predicted increased post-operative pain, presenting evidence of a direct negative effect of self-distraction on long-term physical adaptation (Cohen, Fouladi, & Katz, 2005). Self-distraction may be adaptive in preventing short-term distress, as a study of women within three months of breast cancer diagnosis or six months of completing treatment found that those high in self-distraction were less likely to report problems interacting with health care providers (Collie et al., 2005). Nevertheless, longitudinal research has reported no association of self-distraction and distress in the pre-surgical period, but noted that post-surgical self-distraction was related to increased distress as long as twelve months post-surgery (Culver et al., 2002). It is possible that self-distraction cannot be sustained long-term and prevents the development of other coping strategies.

Denial

A second avoidant coping subtype of interest to this study is denial. A number of conceptualizations of denial exist, but the operational definition for this study is "reports of refusal to believe that the stressor exists or of trying to act as though the stressor is not real" (Carver, Scheier, & Weintraub, 1989, p. 270). Because self-reports of coping efforts were employed in this study, it is crucial to note that the conceptualization of denial

utilized in this study relies on *reports* of denial. Denial, when operationally defined as it is in this study, has correlated with decreased self-esteem, stress hardiness, optimism, and control, and increased anxiety (Carver, Scheier, & Weintraub, 1989). The use of denial as a coping strategy, as well as increased serum cortisol, has shown to be predictive of quicker progression from HIV to AIDS (Leserman et al., 2001). Limited research also suggests that denial is associated with an exaggerated cortisol response (Frecska et al., 1988), though the precise relationship is unclear because just as denial may alter cortisol levels, increased cortisol may inhibit attention to stressors (Frecska et al., 1988).

As a form of avoidant coping, it is perhaps unsurprising that findings similar to those observed in women exhibiting self-distraction coping have also been observed in women using denial coping efforts. The degree to which women report using denial immediately after breast cancer surgery has been shown to be predictive of health worries 12 weeks post-surgery (Wade, Nehmy, & Koczwara, 2005). Exploratory research has yielded denial themes regarding physical symptoms and and medical care in women who have presented with locally advanced breast cancer, a indication of a delay between initial symptoms and the seeking of medical care (Mohamed, Williams, Tamburrino, Wyrobeck, & Carter, 2005).

Behavioral Disengagement

A third subtype of avoidant coping is behavioral disengagement. Behavioral disengagement includes reduction of efforts to deal with the stressor and efforts to achieve goals with which the stressor is interfering, a behavior pattern that is consistent with helplessness (Carver et al., 1989). It is when behavioral disengagement is not

available that strategies such as self-distraction are often utilized. Relationships have been observed between behavioral disengagement, and decreased self-esteem, stress hardiness, type A personality traits, monitoring, social desirability, optimism, and control, and increased anxiety (Carver et al., 1989).

Behavioral disengagement coping is of interest in people with chronic illness partly due to the possible implications for behavioral health. In women diagnosed with breast cancer, behavioral disengagement was related to impaired ability to interact with medical professionals, a finding that suggests the behavioral health of women exhibiting behavioral disengagement could be impaired, as meaningful interaction with medical professional is likely beneficial to adherence to the patient's medical regimen (Collie et al., 2005). Effects of behavioral disengagement on patient symptoms have not been extensively researched, but behavioral disengagement coping was predictive of increased fatigue in a sample of patients with chronic fatigue syndrome, a finding the authors argued as supportive of the need for increased activity levels in these patients (Ray, Jefferies, & Weir, 1997). In a sample of oncological inpatients, behavioral disengagement was among several variables related to impaired performance status, a rating of overall functional impairment (Perez-Aranibar, C., Cordova, H., & Espinoza, M., 2002). Behavioral disengagement may be related to physiological outcomes as well. In adolescents with type one diabetes, behavioral disengagement was related to elevated hemoglobin A1c levels, an indication of sustained harmful elevations in blood glucose levels (Graue, Wentzel-Larsen, Bru, Hanestad, & Sovik, 2004).

Self-Distraction, Denial, and Behavioral Disengagement clustered together in a factor analysis conducted by the author of the Brief COPE in a psychometric study of

these constructs (Carver et al., 1989), lending support to the notion that they are part of a larger avoidant coping category. In all, limited research on the three aspects of avoidant coping of interest to this study indicates that if there is a relationship between each of them and outcomes such as distress, physical symptoms and physiological outcomes, aspects of avoidant coping are generally related to negative outcomes.

Avoidant coping and survival

Some coping strategies that have been investigated as predictors of survival in cancer patients can be categorized, to varying degrees, as avoidant coping strategies. Denial has been defined as "reports of refusal to believe that the stressor exists or of trying to act as though the stressor is not real" (Carver et al., 1989, p. 270). This definition aligns closely with the operationalization of avoidant coping as reducing cognitive and behavioral efforts to deal with the stressor. Use of denial, or of a fighting spirit, as a coping strategy three months post-surgery has been reported to be predictive of increased 10-year survival (Pettingale, 1984), while denial was reported to be predictive of decreased 3-year survival in another study (Achte, Vuhkonen, & Achte, 1979).

A more recent and larger study aimed at replicating Pettingale's (1984) study found that helplessness/hopelessness was predictive of decreased 5-year survival, and no effect of fighting spirit was observed (Watson, Haviland, Greer, Davidson, & Bliss, 1999). However, because these two constructs are conceived by at least one author as bipolar ends of a single continuum, the absence of an association between fighting spirit and survival in this study has been questioned (Greer, 2000). It is interesting to note an

effect of helplessness/hopelessness, a psychological reaction that is consistent with avoidant coping, on survival in a larger and more recent study. Nevertheless, there is no consensus on this issue, and the existing research is not extensive and is likely insufficient to determine the predictive value of self-reported coping and psychological reactions on cancer survival.

Psychosocial Factors and Cancer Incidence

A number of psychosocial variables have been explored as predictors of cancer incidence. Psychosocial factors including marital disruption by divorce, separation, and widowhood have been associated with increased breast cancer incidence (Lillberg et al., 2003). However, several large studies have yielded no effect of psychosocial factors on breast cancer incidence (Lillberg et al., 2001), and one study has found stress to be related to decreased breast cancer incidence (Nielsen et al., 2005). A recent meta-analysis attributed positive findings to statistical evidence of publication bias and concluded that only death of a spouse was substantially related to subsequent cancer incidence independent of publication bias (Duijts, Zeegers, & Borne, 2003).

Psychosocial Factors and Cancer Progression/Survival

Psychosocial factors have also been of interest to researchers investigating survival in patients diagnosed with cancer. In observational studies, longer survival has been linked to social involvement or social support (Hislop, Waxler, Coldman, Elwood, & Kan, 1987; House, Landis, & Umberson, 1988; Maunsell, Brisson, & Deschens, 1995; Reynolds & Kaplan, 1990; Weihs et al., 2005), active coping (Faller, Bulzebruck,

Drings, & Lang, 1999), a "fighting spirit" coping style (Greer, Morris, Pettingale, & Haybittle, 1990), suggesting that psychosocial resources may be involved with disease progression. Other psychosocial factors, including depression (Brown, Levy, Rosberger, & Edgar, 2003), helplessness/hopelessness (Greer, Morris, & Pettingale, 1979) emotional suppression (Reynolds, et al., 2000), and cognitive and behavioral avoidance (Epping-Jordan et al., 1994), have also exhibited relationships with shorter survival.

Observational studies on psychosocial factors and survival have been criticized, with one review of this literature concluding that there was little convincing evidence of a relationship (Petticrew, Bell, & Hunter, 2002). This review cited several studies reporting no significant association between psychosocial factors and cancer survival, with these studies outnumbering those with a significant relationship for most psychosocial factors included in this review. For studies that have not statistically controlled for known potential confounding variables such as age and disease stage (Sainsbury, Anderson, & Morgan, 2000), the validity of significant findings has been questioned. The possibility of publication bias has also been raised, as studies linking psychosocial factors with cancer survival generally had smaller sample sizes than those reporting no significant relationship (Petticrew et al., 2002). Because studies with a larger sample size have greater statistical power to detect a positive relationship, it is surprising that studies with a positive finding have smaller sample sizes. Still, it is unclear whether the oddity in sample sizes is attributable to publication bias. Based on currently available information from observational studies on psychosocial factors and cancer progression, an influence of psychosocial factors on progression can not be confirmed, but trends in this literature are noteworthy. Significant findings reported by observational research have exhibited a

trend toward prolonged survival that is associated with active coping (Faller, Bulzebruck, Drings, & Lang, 1999) and availability of psychosocial resources (Weihs et al., 2005). Conversely, shortened survival has been associated with avoidant coping and symptoms consistent with depressive states. A number of studies have also observed no significant relationship with survival using the same or similar psychosocial variables (Petticrew et al., 2002). Based on these inconsistencies, it seems reasonable to suggest that if a relationship exists between psychosocial variables and survival, it may vary as a function of a number of possible variables such as disease site and stage.

In addition to observational literature on coping and psychosocial resources, the possibility that psychotherapeutic intervention could influence cancer survival has been investigated after randomized prospective trials showed evidence of increased survival time for patients with metastatic breast cancer (Spiegel, Bloom, Kraemer, & Gottheil, 1989) and other cancers (Fawzy et al., 1993; Kuchler, Henne-Bruns, Wood-Dauphinee, Bestmann, & Rappat, 1999), with a survival effect also observed in a mixed cohort study (Richardson, Shelton, Krailo, & Levine, 1990). Although psychotherapeutic intervention targets quality of life improvements, the possibility of prolonged survival as a secondary benefit spawned further research. However, while subsequent interventions have generally achieved the goal of decreasing psychological distress, several psychological interventions in patients with breast cancer have not shown increased survival (Cunningham et al., 1998; Edelman, Lemon, Bell, & Kidman, 1999;Goodwin et al., 2001).

Research into the possibility that psychosocial intervention could prolong survival, in addition to enhancing quality of life, has been controversial. Reviewers have

noted the initial study reporting prolonged survival (Spiegel et al., 1989) was not originally designed with the intention of testing survival and consequently did not have a sufficient sample size for this analysis. As noted by Speigel, Kraemer, and Bloom (1998), larger samples are generally desirable for detecting between-group differences, not for supporting the null hypothesis. Questions have also arisen regarding the use of mean, as opposed to median, survival times in comparing treatment and control groups on the basis that survival curves are typically skewed, suggesting that the median would be a better indicator of central tendency (Coyne, Stefanek, & Palmer, 2007). Although patients were randomized to treatment and control groups in this study, subsequent review argued that the control group was anomalous because the survival times of these patients were lower than geographically-matched women with metastatic breast cancer from an available database (Fox, 1998). Though this is an interesting and useful hypothesis, but it is important to keep in mind that a control group assigned randomly from within the study sample is a more internally valid comparison group than a community database (Spiegel, Kraemer, & Bloom, 1998). Randomization is the preferred method for eliminating bias in group selection. Despite the best efforts of researchers, the samples that comprise interventions are treatment-seeking individuals that are willing to participate in research and may systematically vary in other ways that are different from the population of all patients in the community with cancer.

Two meta-analyses of psychosocial intervention and survival have been published. Chow, Tsao, and Harth (2004) found no effect of intervention on 1-year or 4-year survival for all cancers or for metastatic breast cancer, in particular. This report noted that the available data were insufficient for evaluating a small effect size for

survival (Chow et al., 2004). Another meta-analysis found that individual, but not group, interventions exhibited a significant effect on prolonged survival, though only three studies of individual therapy were included in this analysis (Smedslund & Ringdal, 2004). Spiegel and Giese-Davis (2003), in their review of studies on group therapy and survival, found that 5 of 10 studies reported a prolonged survival effect, and no studies reported a survival deficit related to psychotherapeutic intervention. More recent randomized prospective trials have also found no effect of psychotherapeutic intervention on survival (Goodwin et al., 2001; Kissane et al., 2007; Kissane et al., 2004). The absence of a survival effect in a majority of studies questions the robustness of the survival effect. It has been noted that the proportion of studies finding an effect of psychosocial intervention on survival is greater than the proportion expected to be observed by chance alone (Spiegel, 2002). In addition, no trials have reported decreased survival for the treatment group, as compared to the control group, a further departure from the expected pattern if no relationship existed between psychosocial intervention and survival. Still, the possibility of publication bias in favor of positive results exists (Palmer & Coyne, 2004).

Similarly, intervention research has produced inconsistent results. Based on the existing data, a robust, moderate or large effect of psychotherapeutic intervention on survival seems unlikely, but an effect of psychotherapeutic intervention on survival that is small or restricted to certain conditions may be present. One striking trend in research on a survival effect is that trials reporting a significant survival effect were generally conducted longer ago, with more recent trials noting no survival advantage (Goodwin et al., 2001;Kissane et al., 2007; Kissane et al., 2004; Spiegel et al., 2007). Spiegel (2002)

commented that medical treatments and outcomes have advanced significantly since the initial trials were conducted. Concurrently, support group availability and public awareness and support of women with breast cancer have increased. As a result, the variance in survival previously contributed by intervention may now be provided by available social support and medical care.

In further reviewing the interventions that exhibited prolonged survival effects, among the common elements specified as "necessary but not sufficient" (Spiegel, 2002) for producing beneficial survival was quality of life improvement. In line with the emphasis on quality of life improvement, the learning of coping skills was identified as an essential component to interventions that may provide a survival benefit (Spiegel, 2002). Quality of life improvement is interesting in part because this was the achieved target outcome for the initial trial that reported survival benefits for treatment participants (Spiegel & Bloom, 1981), and an intervention that did not improve quality of life would not be expected to improve survival (Coyne, Stefanek, & Palmer, 2007). The promotion of quality of life improvements seems appropriate as a primary target of psychotherapeutic intervention for patients with cancer regardless of the conclusion provided by research into associated survival benefits.

The absence of a survival effect in more recent randomized trials with breast cancer patients presents compelling evidence that there is no current survival effect, though it may have been present prior to alterations in the culture surrounding breast cancer diagnosis and treatment. Improvement in quality of life outcomes underscore the utility of continued psychosocial intervention and presents an opportunity for needed research into increased survival as a secondary benefit of intervention.

Coping Mechanisms Targeted by Interventions

One motivation for investigating coping is that coping skills training has often been a component of psychosocial interventions with demonstrated effectiveness (Antoni, Wimberly, et al., 2006). Successful psychosocial interventions in patients with breast cancer have generally incorporated active coping strategies, presumably to replace avoidance strategies. The act of engaging in a psychosocial intervention is essentially a form of active coping in the sense that the patient likely expects to confront the diagnosis of breast cancer and reactions to the diagnosis.

Interventions for patients with breast cancer have aimed to enhance social support. In most group interventions, patients likely benefit from the social support provided by other group members (Spiegel & Diamond, 2001). Social support can consist of instrumental support that provides advice, assistance, or information. Social support can also be useful in ameliorating the effects of breast cancer through the provision of emotional support. The social support from group therapy provides the opportunity to interact with other people that are facing similar stressors and are typically more comfortable discussing breast cancer-related distress and fears of death and dying (Spiegel & Diamond, 2001).

Supportive expressive group therapy (SET), one treatment used in breast cancer patients, facilitates emotionally expressive discussion on fears of dying and death, reordering life priorities, improving support from and communication with family and friends, integrating a changed self and body image, and improving communications with physicians (Spiegel & Classen, 2000). By facilitating emotional expression, SET

promotes active coping in that patients engage with the emotional effects of the stressor, breast cancer. Research has supported the usefulness of coping with cancer through actively processing and expressing emotions (Stanton et al., 2000). Emotional expression may benefit patients through a decrease in the use of avoidant coping strategies such as suppression (Giese-Davis et al., 2002) and repression as coping methods (Spiegel & Diamond, 2001).

Finding meaning is relevant to coping with cancer in light of the existential concerns presented when diagnosed with a life-threatening illness. Park and Folkman (1997) extended the transactional model of stress and coping to include meaning-making coping, conceptualizing it as "a coping process that is initiated by recognition of a discrepancy between an individual's appraised personal significance of an event and that individual's global beliefs" (p. 121). They described the resolution of these discrepancies through 1) reappraisal of an event to assimilate it into the existing global meaning structure, or 2) modifying the global meaning structure in a way that is consistent with the event. Because this process requires active cognitive processing of the event, situational meaning, and global meaning, avoidant coping that reduces awareness of the stressor is a barrier to meaning-making coping. In contrast, emotional expression regarding existential concerns is central to SET, as well as other interventions for patients with breast cancer (Chan et al., 2006; Classen et al., 2001; Lee, Cohen, Edgar, Laizner, & Gagnon, 2006;Spiegel et al., 1989). This focus on existential concerns may allow meaning-making coping to take place.

Social-cognitive theory (Bandura, 1986) emphasizes reciprocal interactions between the person, behavior, and the environment in explaining the acquisition and

maintenance of behavior patterns. Social-cognitive theory includes the concept of self-efficacy, a person's confidence in his or her ability to perform a specific behavior (Bandura, 1977). Because self-efficacy for a given behavior is a strong predictor of the person's exhibiting that behavior (Bandura, 1977), it is a variable of interest. SET has increased patients' self-efficacy to focus on and enjoy the present (Fobair et al., 2002). Self-efficacy for enjoying the present describes an individual that feels confident in producing positive, present-focused experiences, which is more characteristic of active coping. Because avoidant coping is incompatible with self-efficacy, an increase in self-efficacy is consistent with active coping, but it should be noted that self-efficacy is not classified as a coping method.

It is also noteworthy that didactic teaching of coping skills is not part of SET. Rather, active coping strategies such as seeking social support, emotional expression, and cognitive reappraisal seem to be integrated into the treatment process, and these activities are inconsistent with the use of avoidant coping strategies. Regarding outcomes, patients in SET interventions have exhibited evidence of treatment gains including reductions in trauma symptoms (Classen et al., 2001; Fobair et al., 2002; Spiegel et al., 1999), a target of particular interest in patients with breast cancer. Patients participating in SET have also reported decreased mood disturbance (Classen et al., 2001; Fobair et al., 2002; Goodwin et al., 1998; Goodwin et al., 2001; Spiegel & Bloom, 1981; Spiegel et al.,1999) and anxiety (Fobair et al., 2002; Spiegel & Bloom, 1981; Spiegel et al., 1999), presenting evidence that the coping strategies embedded within this therapy may influence psychiatric morbidity. SET has also exhibited evidence of effectiveness in quality of life variables such as improved sleep (Fobair et al., 2002) and reduced pain

(Fobair et al., 2002; Goodwin et al., 2001; Spiegel & Bloom, 1981). Finally, participation in SET may promote improved nutrition (Goodwin et al., 1998).

In addition to SET, other interventions have been used in a number of studies of patients with breast cancer. Mindfulness-Based Stress Reduction (MBSR; Kabat-Zinn, 1990) is an intervention that utilizes meditation, yoga, focus on body sensations, and group processes to cultivate mindfulness, a nonjudgmental awareness of moment to moment experiences. MBSR includes discussion of mindfulness and acceptance, and formally includes relaxation techniques such as yoga as part of the intervention. MBSR also utilizes a body scan technique that encourages focus on physical sensations, even those that are aversive and that patients may attempt to block from consciousness.

There is no consensus on the ways in which MBSR maps onto traditional conceptualizations of coping, but there is some available research literature on the topic. Activities such as meditation, yoga, and the body scan practiced in MBSR could be employed in response to stressors and would provide a concrete active coping effort to patients. Because avoidant coping involves attempts to remove distressing thoughts from consciousness, the promotion of awareness that permeates MBSR runs counter to many avoidant coping efforts. One study investigating the use of coping strategies in MBSR participants has supported the notion that they generally report increased active coping and decreased avoidant coping (Wilson, 2006). Examination of an intervention study has revealed that the increased use of acceptance associated with participation in this intervention mediated improved hemoglobin A1c levels in patients with diabetes (Gregg, Callaghan, Hayes, & Glenn-Lawson, 2007). Patients in MBSR interventions have exhibited evidence of treatment gains including reduced stress (Carlson, Speca, Patel, &

Goodey, 2003; Carlson, Speca, Patel, & Goodey, 2004), improved quality of life (Carlson et al., 2003) (Carlson et al., 2004), sleep (Carlson et al., 2003), and changes in the production of cytokines (Carlson et al., 2003), an essential component of the immune system.

Cognitive-behavioral therapy (CBT) has also been implemented for women with breast caner. CBT is based on the idea that there are interactions between thoughts, behaviors and emotions. This treatment orientation is the one most closely aligned with the promotion of coping skills to be used in addressing stressors, and coping skills are sometimes taught in a didactic manner. Confidence in these coping skills has shown evidence of mediating the effect of intervention on quality of life outcomes, suggesting that coping is essential to the relationship between the diagnosis of breast cancer and clinically relevant outcomes (Antoni, Lechner, et al., 2006).

Several CBT interventions with breast cancer patients have formally incorporated problem solving coping strategies (Cimprich et al., 2005; Doorenbos et al., 2005). Problem solving is a domain of coping that encompasses several subsets of coping efforts directed at altering the stressor (Carver et al., 1989). Problem solving typically consists of assessment of the problem, generation of possible actions aimed at solving or altering the problem, decision making, and implementation of the chosen plan (D'Zurilla & Nezu, 2001). Behavioral health goals such as smoking cessation, enhanced nutrition, and increased physical activity have been targeted in breast cancer patients. This strategy can be seen as a form of problem solving coping in the context of physical illness because this coping strategy addresses the stressor, breast cancer, which is likely appraised by the patient as threatening or harmful to her health, through health-promoting behavior.

Methods of promoting relaxation are often provided in CBT interventions. These strategies are typically suggested as methods of coping with and reducing anxiety (Antoni, Wimberly, et al., 2006). Muscle relaxation and relaxing imagery techniques have been used with patients with breast cancer (Antoni, Wimberly, et al., 2006). Muscle relaxation typically consists of alternating tensing and relaxing of major muscle groups, while imagery typically consists of visualizing a relaxing situation (Greenberger & Padesky, 1996). These strategies are intended to arm patients with a way to ameliorate the anxious symptoms associated with breast cancer, preparing patients to cope with the stressor. The ability to enact active coping responses provides a viable alternative to avoidant coping strategies. Consequently, the frequency of avoidant coping strategies may be reduced.

Reappraisal of stressors, as described above, is another coping skill that has been included in CBT interventions in patients with breast cancer (Antoni, Wimberly, et al., 2006; Northouse, Kershaw, Mood, & Schafenacker, 2005). Improved communication skills aimed at enhancing social support are also formally taught in CBT interventions (Andersen et al., 2006)

Breast cancer patients in CBT interventions have exhibited evidence of treatment gains including reduced breast cancer-related intrusive thoughts (Antoni, Wimberly, et al., 2006). Available research also suggests that CBT is effective in reducing anxiety (Antoni, Wimberly, et al., 2006; Cimprich et al., 2006), general distress (Simpson, Carlson, & Trew, 2001; Tatrow & Montgomery, 2006), providing additional support for the notion that active coping strategies are related to decreased psychiatric symptomatology. Studies of CBT with breast cancer patients have noted improved pain

experience (Arathuzik, 1994; Tatrow & Montgomery, 2006), reduced social disruption (Antoni, Lechner, et al., 2006), decreased limitations associated with cancer-related symptoms (Doorenbos et al., 2005), and decreased serum cortisol (Cruess et al., 2000); improvements in mood (Antoni, Lechner, et al., 2005; Lewis, Casey, Brandt, Shands, & Zahlis, 2006; Simpson et al., 2001), perceived social support (Andersen et al., 2004; Cimprich et al., 2005), behavioral health (Andersen et al., 2004; Cimprich et al., 2005), treatment adherence (Cimprich et al., 2005), and quality of life (Simpson et al., 2001), increased perceptions of benefits related to breast cancer (Antoni, Lechner, et al., 2006; Cruess et al., 2000; McGregor et al., 2004), and improvements in indicators of immunity (Andersen et al., 2004; McGregor et al., 2004).

Daily Assessments

One feature of the transactional model of stress is that coping outcomes are likely to affect appraisals or future coping efforts. Successful coping efforts might lead to decreased stress appraisals, while unsuccessful coping efforts might lead to increased stress appraisals and altered coping strategies. As this process is repeated, memories of coping efforts will be expected to be altered. The transactional model predicts that success or failure of coping efforts would alter the stressor, stressor-relevant appraisals, and subsequent coping efforts. Thus, assessments of coping are likely to be highly dependent on the time of assessment (Tennen & Affleck, 1996). A stressor could initially be countered using denial, but after the stressor persists for several days, problem-solving strategies could be used. If problem solving proves unsuccessful, the individual may cope by seeking emotional social support. The coping method reported by this individual could

be denial, problem-solving, or seeking social support depending on the time of assessment. Further, a trait-oriented assessment asking for a retrospective report of the person's typical coping strategy may yield a commonly employed coping effort. However, this coping effort may not be used in response to the stressor of interest in a given situation. The discrepancy between retrospective and daily assessments of health-relevant information is supported by recall bias in chronic pain (Erskine, Morley, & Pearce, 1990; Larsen, 1992) and panic attacks (Margraf, Taylor, Ehlers, Roth, & Agras, 1987; Rapee, Craske, & Barlow, 1990). In the same population, comparisons between retrospective and daily assessments found that infrequently employed coping strategies were significantly less likely to be recalled in retrospective reports as opposed to daily assessments (Porter & Stone, 1996).

While many valuable findings have emerged from the coping literature, research methods have in some ways been inconsistent with the transactional model of stress (Lazarus, 2000). The rapidly fluctuating stress, coping, and adaptation process proposed by this model suggests that retrospective report may be clouded by the success or failures of coping efforts employed over the period of time for which respondents are reporting. In response to this problem, coping assessments have been developed that focus on measuring the coping process over a period of consecutive days. For example, diaries and other self-report measures can be used to assess dynamic processes, such as day-to-day coping. Use of such measures minimizes retrospective reporting bias due to assessments that occur closer to the time of occurrence (Tennen & Affleck 1996). Furthermore, individual data sets can be aggregated and group trends studied, preserving the strengths of a nomothetic design.

Cortisol Rhythms

Stress-related cortisol secretion has often been measured by noting the total cortisol secretion in a given period of time or the cortisol level at one point during the day (Kirschbaum & Hellhammer, 1994). Another marker of HPA axis activity is the deviation of circadian cortisol rhythms. In approximately 90% of healthy people, cortisol levels begin to rise immediately prior to awakening, peak 30-45 minutes after awakening, and decrease slowly throughout the rest of the day (Posener, Schildkraut, Samson, & Schatzberg, 1996). Diurnal cortisol slopes have been reported to exhibit significant variation between individuals, with a small proportion of healthy individuals exhibiting flat slopes (Stone et al., 2001).

Perhaps due to the sensitivity of the HPA axis to stress appraisals, studies have observed an association of psychosocial variables with disrupted circadian physiological functioning (Antoni, Lutgendorf, et al., 2006). In two different samples of patients with metastatic breast cancer, lower perceived social support was related to disrupted circadian cortisol slopes (Abercrombie et al., 2004; Turner-Cobb, Sephton, Koopman, Blake-Mortimer, & Spiegel, 2000). Depression has been linked with persistently elevated cortisol levels throughout the day (Deuschle et al., 1997). In another study, participants who were unemployed exhibited significantly decreased evening cortisol levels relative to their employed counterparts (Ockenfels et al., 1995). While findings are mixed, a number of studies have found that people with PTSD exhibit diminished total daily cortisol secretion and disrupted circadian cortisol profiles marked by a flattened diurnal cortisol slope (Miller, Chen, & Zhou, 2007), without the morning elevations and evening nadir characteristic of many healthy individuals (Posener et al., 1996).

Intrusions and Physiology

As a type of distress, it is not surprising to note that intrusions are associated with alterations in physiology. The presence of breast cancer-specific intrusions was associated with elevated cortisol during the work period in healthy women (Dettenborn, James, Valdimarsdottir, Montgomery, & Bovbjerg, 2006). In Three Mile Island-area residents, disaster-specific intrusions were associated with increased cortisol, epinephrine, norepinephrine, and cortisol obtained by collecting urine between 6 p.m. and 9 a.m. Intrusions were also related to increased heart rate and systolic blood pressure (Davidson & Baum, 1986). Intrusions have also been linked with immunosuppression in students anticipating an examination (Workman & La Via, 1987). In addition, in men undergoing testing for HIV, intrusions were correlated with increased plasma cortisol on the day of sample collection at 1 week, 3 weeks, and 5 weeks after being informed of test results. To reduce confounding from diurnal variation in cortisol values, blood samples were provided by fasting participants between 7:30 a.m. and 10:30 a.m. (Antoni et al., 1990). Finally, men that were within 1.5 years of returning from Operation Desert Storm combat in Iraq exhibited evidence of a relationship between increased intrusions and hypersensitivity to inhibition of cortisol secretion, one indicator of HPA axis dysfunction. (Kellner, Baker, & Yehuda, 1997). Sensitivity to inhibition of cortisol secretion was tested with the administration of a synthetic steroid called dexamethasone the night prior to saliva collection. Because dexamethasone inhibits ACTH production, it typically suppresses the level of cortisol secreted the following morning. The dexamethasone test is used to assess the response of the HPA axis to inhibitory mechanisms (Kirschbaum & Hellhammer, 1994). Taken together, these reports point to intrusions as a variable of

particular interest in research on the effects of psychological distress on physiology, specifically cortisol.

Circadian Cortisol Rhythms and Trauma

While the majority of research has supported the notion of increased cortisol secretion in response to stress, the majority of studies of individuals that have been exposed to traumatic events and developed PTSD have observed decreased cortisol secretion (Miller et al., 2007). However, conflicting results have been noted across studies. Yehuda (2002) reviewed studies of cortisol and trauma and concluded that individuals exposed to trauma exhibited normal morning elevations in cortisol, but a lower nocturnal cortisol nadir. A more recent meta-analysis found that individuals with PTSD were characterized by consistently decreased cortisol output throughout the day, with a flat diurnal slope. This review also found that time since the traumatic event was negatively correlated with overall cortisol output and attributed conflicting findings to variability in time since the stressor (Miller et al., 2007) Among the studies included in this meta-analysis, the length of time since the trauma ranged from 1-720 months.

The distinct diurnal cortisol profiles of people with PTSD could be related to the unique features of this disorder. The Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV; APA, 1994), criteria include a response of "intense, fear, helplessness, or horror" to the traumatic event. The DSM-IV criteria also specify that the individual re-experiences the event, suggesting that the intense responses that occurred during the original event recur during the course of the disorder. The typical diurnal cortisol profile has been conceptualized as healthy cortisol output for an individual that is

not experiencing stress (Miller et al., 2007) because the decrease in cortisol throughout the day allows for healing and growth following a short-term adaptation to awakening through a cortisol increase (Epel & McEwen, 1998). In contrast, the flattened diurnal cortisol slope characteristic of individuals who have experienced a traumatic event and of patients with breast cancer could be viewed as an adaptive response to a chronic stressor in that the individual must have energy available at all times to counter the stressor and can not afford a decrease in cortisol throughout the day (Miller et al., 2007). Nevertheless, a constant level of cortisol throughout the day has several potential costs. First, invariability of cortisol availability could render the person less able to mount an increased response to an acute stressor (Epel & McEwen, 1998). Second, the allostatic load that can occur with chronic overactivation of the HPA axis could leave the person vulnerable to illness onset or progression (McEwen & Stellar, 1993). Perhaps most importantly, the disruption of circadian rhythmicity itself may be associated with illness onset or progression (Antoni, Lutgendorf, et al., 2006).

Circadian Rhythms and Cancer

Although not studies of cortisol rhythms, several studies of women with abnormal circadian activity rhythms have supported a link of these rhythms with elevated breast cancer vulnerability (Davis, Mirick, & Stevens, 2001; Pukkala, Auvinen, & Wahlberg, 1995; Schernhammer et al., 2001). Disruption of circadian rhythms has been identified as one possible contributor to the increased breast cancer incidence observed in women whose occupations expose them to light at night time, resulting in an abnormal pattern of activity and environmental stimuli. These large, epidemiological studies typically

matched women with breast cancer diagnoses to control cases to compare the groups in terms of night shift work. In one study, 7,035 Danish women employed in various occupations that required work at night for at least one year exhibited elevated breast cancer incidence as a group when compared to matched, employed control women (Hansen, 2001). Additionally, within the sample of night shift workers in this study, increased night shift work was related to increased breast cancer incidence. Similar findings were reported in a study of 78,562 nurses in the United States that worked at least three night shifts per month for at least one year. This study found that nurses working at least 30 years of night shifts had increased breast cancer incidence relative to nurses that had never worked rotating night shifts (Schernhammer et al., 2001). Night shift work was also related to breast cancer incidence in a study matching women in the United States diagnosed with breast cancer to age-matched controls recruited through random-digit dialing (Davis et al., 2001).

Prior to these studies on breast cancer incidence in women performing shift work, a study of Finnish flight attendants examined the relationship between this occupation and breast cancer incidence. These flight attendants exhibited an elevated rate of breast cancer incidence relative to the rate observed in the general population (Pukkala et al., 1995). Although circadian disruption was not proposed as the mechanism for increased incidence in this study, flight attendants often perform night shift work and are exposed to inconsistent light/dark rhythms due to travel, suggesting circadian disruption as a possible mechanism. As a whole, these studies support the relevance of sleep/wake rhythms in cancer incidence. The precise mechanism of the connection between

sleep/wake rhythms and breast cancer incidence is not established. Also of interest is the question of whether sleep/wake rhythms and cancer progression influence one another.

The circadian physiological system is influenced by melatonin, a hormone secreted by the pineal gland, which registers the amount of light taken in by the eye. Using this input, the pineal gland alters the sleep-wake cycle by secreting more melatonin when it registers less light, thus cueing sleep. Melatonin levels typically peak at night and suppress estrogen production, but exposure to light inhibits the melatonin peak. As a result, night shift work may lead to increased estrogen in the body, a factor related to increased risk of breast cancer (Davis et al., 2001). Thus, melatonin is one possible mechanism for the observed effect of night shift work on breast cancer incidence (Bartsch & Bartsch, 2006; Stevens, 2006). While this mechanism is promising, other possible effects of circadian disruption could also bring about alterations in cancer incidence.

An estimated 30-70% of patients with breast cancer exhibit disruption of circadian cortisol rhythms marked by limited diurnal variation, elevated cortisol secretion throughout the day, or erratic profiles (Sephton & Spiegel, 2003). Flattened diurnal cortisol rhythms have been demonstrated in women with breast cancer (Abercrombie et al., 2004; Carlson et al., 2004) as well as a sample consisting of patients with cancer at varied sites (Touitou, Bogdan, Levi, Benavides, & Auzeby, 1996). Cancer patients also have altered metabolic, immunologic and rest-activity rhythms with greater circadian disturbance in more advanced cases (Mormont & Levi, 1997).

The ability of circadian cortisol rhythms to predict disease progression was investigated in women with metastatic breast cancer that were recruited to participate in a

trial of Supportive/Expressive group therapy (SET). These women provided saliva samples at 8am, noon, 5pm, and 9pm on three consecutive days prior to randomization to treatment or control groups. This allowed for calculation of a diurnal cortisol slope by regressing collection times on cortisol values. A flatter diurnal cortisol slope, in contrast to the decrease in cortisol levels throughout the day that is characteristic of circadian rhythmicity, was a significant predictor of mortality in this sample (Sephton, Sapolsky, Kraemer, & Spiegel, 2000). This effect was independent of immune factors including the numbers and activity of natural killer (NK) cells, an immune cell type that is particularly important in tumor resistance. Other variables correlated with the diurnal cortisol slope were statistically controlled in subsequent analyses. These variables included metastasis to the chest wall or lymph nodes, as opposed to bones or internal organs, taking the medication megestrol, nocturnal awakenings, and marital disruption. The predictive ability of the diurnal cortisol slope was independent of each of the potential confounds tested. The effect of the diurnal cortisol slope on survival was also independent of the effects of common prognostic factors including age at diagnosis, estrogen receptor status, and disease-free interval (Sephton et al., 2000). Survival was assessed an average of 5.9 years (range = 3.1-7.7) after cortisol data were collected. The robust relationship between the diurnal cortisol slope and survival identified circadian cortisol rhythms as an important variable for future research.

Interestingly, the circadian cortisol rhythm was not retained in a model predicting prolonged survival using clinical predictors and the rest-activity rhythm. Additionally, the rest-activity measure employed in this study was not significantly associated with the circadian cortisol rhythm. This finding stands in contrast to the studies reviewed above

reporting an association between sleep and circadian cortisol rhythms. Part of the explanation for this finding may lie in the methodology. Serum samples used to measure the circadian cortisol rhythm were collected at 8 a.m. and 4 p.m. on two consecutive days. The circadian rhythm was estimated by subtracting the 4 p.m. value from the 8 a.m. value to yield a difference score for each subject (Mormont et al., 2000). The study reporting the diurnal cortisol slope as a predictor of survival in patients with metastatic breast cancer sampled saliva on three consecutive days at four time points: 8 a.m., noon, 5 p.m. and 9 p.m. (Sephton et al., 2000). The circadian rhythm was operationally defined by a diurnal slope derived from a regression of cortisol values on collection times. The latter design benefits from an additional day of collection, and the added sampling times likely increased the reliability of the assessment of the diurnal rhythm (Kraemer et al., 2006). The collection of four samples throughout the day also offers potential benefit because of added variability assessed in cortisol secretion. In addition, because the 4 p.m. sample in the Mormont et al. study was the final sample taken, the evening nadir characteristic of typical cortisol profiles was replaced in this analysis by an afternoon value (Mormont et al., 2000). This reduced variability could have contributed to limited predictive ability of the circadian cortisol rhythm and the absence of an association with the rest-activity rhythm (Mormont et al., 2000). Saliva samples assess the level of free cortisol, the amount that is unbound and active. Because serum samples assess the total cortisol level, variance in circadian cortisol rhythms is introduced by the sampling method employed. Finally, the regression slope employed in the Sephton et al. (2000) study fits well with the concept of changes in cortisol availability with respect to time throughout the day, while the difference between the two values employed in the

Mormont et al. study indicates the magnitude of the difference between these two measurements. Still, it is unclear whether differing methodologies account for the lack of an association between rest-activity and circadian cortisol rhythms in this study.

Animal studies have also supported a relationship between circadian rhythms and cancer progression. In mice, mutations to genes essential to circadian rhythmicity are related to faster tumor progression (Fu & Lee, 2003; Fu, Pelicano, Liu, Huang, & Lee, 2002). Similarly, destruction of the murine suprachiasmatic nuclei that control circadian rhythms of motor activity and adrenocortical secretion has produced faster tumor progression (Filipski et al., 2002).

Research on the diurnal cortisol decrease has been complemented by research on the cortisol awakening response (CAR). These studies focus on the rise in cortisol that typically follows awakening. An increased CAR has been linked with stress (Schlotz, W., Hellhammer, J., Schulz, P., & Stone, A., 2004) and symptoms of depression (Pruessner, Hellhammer, Pruessner, & Lupien, 2003). Conversely, a diminished CAR has been linked with PTSD (Rohleder, Joksimovic, Wolf, & Kirschbaum, 2004), poor sleep in patients with insomnia (Backhaus, Junghanns, & Hohagenet al., 2004), people with chronic fatigue (Roberts, Wessely, Chalder, Papadopoulos, & Cleare, 2004), clinical depression (Huber, Issa, Schik, and Wolf, 2006), and job burnout (Pruessner et al., 1999).

Cortisol typically reaches its nadir early in the evening, with a rise shortly prior to awakening (Wilhelm, Born, Kudielka, Schlotz, Wust, 2007). Under laboratory conditions, an increase in cortisol during the period immediately preceding awakening was negatively correlated with the CAR (Wilhelm et al., 2007). These results may be reconciled with research indicating that a later awakening time is associated with a

decreased CAR in nonclinical samples (Stetler & Miller, 2005). With this in mind, an increased CAR could be indicative of disrupted circadian rhythmicity marked by an insufficient pre-awakening cortisol rise. However, the majority of CAR studies have concluded that the CAR is driven by awakening, rather than by circadian cortisol rhythms, suggesting no effect of sleep variables on the CAR aside from the time of awakening (Hucklebridge, Clow, Rahman, & Evans, 2000; Stetler & Miller, 2005).

In contrast to studies suggesting that disruption of circadian rhythms may pose a risk of cancer and stress-related conditions, new data present the potentially positive effects of circadian regulation, suggesting that normalizing circadian periodicity may promote tumor defense and enhance treatment effects (Fu & Lee, 2003). A cognitive-behavioral stress management intervention has resulted in reductions in serum cortisol in breast cancer patients (Cruess et al., 2000), and a behavioral intervention also observed reduced serum cortisol in patients randomized to the treatment group (Schedlowski, Jung, Schimanski, Tewes, & Schmoll, 1994). Patients with breast cancer who participated in a mindfulness-based stress reduction (MBSR) intervention also reduced saliva cortisol levels at post-treatment, but only for those patients with elevated cortisol at the outset of the study (Carlson et al., 2004), an effect also observed in plasma cortisol in an experiential-existential group therapy intervention (van der Pompe, Duivendoorden, Antoni, Visser, Heijnen, 1997). In the MBSR study, a reduction of cortisol in patients exhibiting patterns marked by abnormally high afternoon values was also observed (Carlson et al., 2004). A meditation intervention in healthy male adults resulted in lowered morning basal cortisol levels and increased reactivity of cortisol to laboratory stressors (MacLean et al., 1997). Increased responsivity to an acute stressor is likely a

healthy endocrine response enabling short-term adaptation to environmental demands (Epel & McEwen, 1998). Given more recent results underscoring the importance of the circadian rhythm, future interventions measuring cortisol could investigate whether reductions in overall cortisol are accompanied by regulated circadian cortisol rhythms.

Given these findings, the possible role of circadian disruption as a mechanism for explaining the negative effects of psychosocial variables on disease is an important area of research. The role of coping in mitigating deleterious effects of stress on circadian disruption and quality of life is also in need of clarification.

Circadian Disruption in Response to Acute Stressors

Although conceptualizations of the destructive effects of stress on physiological responses have often focused on the wear and tear that may result from exposure to chronic stressors, disruption of circadian rhythms can also result from acute stressors. High intraindividual variability in the morning cortisol increase and diurnal cortisol slope has been noted between consecutive days of saliva sampling (Kraemer et al., 2006). The morning cortisol increase, in particular, has been found to be sensitive to psychological states such as stress (Hellhammer et al., 2007). This suggests that diurnal cortisol profiles are responsive to acute events or psychological states, as opposed to being stable characteristics that are only altered slowly over time.

Implications of Circadian Disruption

Further research is needed to clarify the implications of disrupted circadian cortisol and rest-activity rhythms. These disruptions may be implicated in a poor

response of this system to acute environmental stressors. This view is supported by studies indicating altered circadian cortisol profiles in patients reporting depression (Giese-Davis, et al., 2006; Lupien et al., 1999), a condition that typically incorporates perceptions of helplessness and hopelessness, as well as inactivity. Similarly, laboratory studies have noted a blunted cortisol response to social stressors (Burke, Davis, Otte, & Mohr, 2005) and a blunted response to administration of a corticosteroid medication called dexamethasone in those reporting depression (Burke et al., 2005; Giese-Davis et al., 2006).

In recent work on circadian cortisol rhythms in women with breast cancer, a flattened diurnal cortisol slope appeared to be related primarily to elevated evening cortisol levels, with no relationship observed between the diurnal slope and awakening levels. However, a flatter diurnal slope was associated with a more dramatic cortisol increase in the 30 minutes after awakening. It should be noted that the awakening cortisol value, and not the 30 minute post-awakening value, is used in calculating the diurnal cortisol slope. In addition, the diurnal slope was not significantly associated with social stress produced by the Trier Social Stress Test, suggesting that disrupted rhythms are not due to acute stress. Rather, a flattened diurnal cortisol slope was associated with diminished suppression of morning cortisol secretion in response to dexamethasone administration. Dexamethasone acts on inhibitory mechanisms that reduce the secretion of ACTH by the pituitary gland and, subsequently, the secretion of cortisol by the adrenal gland. Because dexamethasone administration is expected to decrease cortisol secretion, the blunted response in patients reporting depression suggests disruption of the HPA axis.

Taken together, these findings suggested that the exaggerated cortisol response to awakening and sustained cortisol secretion throughout the day was due to impaired negative feedback inhibition (Spiegel, Giese-Davis, Taylor, & Kraemer, 2006). A study dividing patients with metastatic breast cancer into a group with a depressive disorder or taking antidepressant medication and a group without depression also found that depression was unrelated to cortisol reactivity to the Trier Social Stress Test. Patients with depression did exhibit an exaggerated awakening cortisol response, though no other relationships with circadian cortisol rhythms were observed (Giese-Davis et al., 2006). Considering previous work linking a flattened diurnal cortisol slope with an exaggerated awakening response, it is interesting to note that distress, depression in this case, may influence this circadian disruption. Finally, in a subset of women with metastatic breast cancer, emotional expression during the first session of group therapy (SET) was related to a steeper diurnal cortisol slope. It should be noted that saliva samples for cortisol assay were provided prior to the initiation of treatment, suggesting that it is the propensity to express emotion, rather then the expression that occurred in the videotaped session, that was related to a more rhythmic diurnal cortisol profile (Giese-Davis, DiMiceli, Sephton, & Spiegel, 2006). This finding builds on the observation that depression may be related to disruption of circadian cortisol rhythms by suggesting that active coping, specifically emotional expression, may be associated with a more normalized circadian cortisol rhythm.

The sustained hypersecretion of cortisol characteristic of people with depression has been observed in several studies of patients with cancer (Andersen, 2002), including gynecological (Evans, McCartney, Nemeroff, 1986) and pancreatic cancer (Joffe,

Rubinow, Denicoff, Maher, & Sindelar, 1986). These blunted responses to acute stressors suggest impairment of the HPA axis to be responsive to environmental demands. If an individual lacks the physiological response needed to cope with an acute stressor, adaptation could be compromised. Conversely, if the HPA axis does not inhibit cortisol secretion in response to physiological cues, overexposure to cortisol and catabolic processes may suppress immunity and break down muscle tissue.

Stress-related disruption of circadian rhythms may also reduce the effectiveness of chronomodulated chemotherapy. Chronomodulated chemotherapy attempts to target tumors with chemotherapeutic drugs at a point in the day at which normal cells are not expected to be actively mitotic to minimize the side effects on these cells. If circadian rhythms are disrupted, the expected benefits of this method of administration would be eliminated (Sephton & Spiegel, 2003).

A recent review and meta-analysis of cortisol research has described the condition under which cortisol profiles become flattened. This review concluded that a stressor that is threatening to physical integrity, traumatic, and uncontrollable is most likely to elicit a flattened diurnal cortisol profile (Miller et al., 2007). A diagnosis of breast cancer typically has these features. A diagnosis of metastatic breast cancer may fit particularly well with these features because advanced disease likely promotes a sense of imminent threat and uncontrollability. These conceptualizations lend coherence to the robust predictive effect of the diurnal cortisol slope on survival in patients with metastatic breast cancer (Sephton et al., 2000). It is important to note that Miller et al.'s assertions regarding disruption of circadian cortisol rhythms suggest that distress and appraisals regarding the stressor are related to circadian disruption, as opposed to circadian

disruption driven exclusively by physiological effects of chronic illness. Primary breast cancer also threatens physical integrity, though likely to a lesser extent. Cancer is a life-threatening illness and produces elevations in intrusions (Bleiker, Pouwer, van der Ploeg, Leer, & Ader, 2000). Although medical treatments offer a chance at remission and psychosocial interventions and coping can influence the effects of cancer on quality of life, cancer can only be controlled to a limited extent. Consequently, alterations in circadian cortisol rhythms are of particular interest in women with breast cancer.

Sleep Disruption in Breast Cancer

Patients with breast cancer have consistently reported sleep disturbance (Payne, Piper, Rabinowitz, & Zimmerman, 2006). This sleep disturbance has included difficulty with sleep onset and maintenance, as well poor sleep quality (Roscoe et al., 2007). At least one form of sleep disturbance was reported by 63% of women with metastatic breast cancer (Koopman et al., 2002). Of these sleep concerns, nocturnal awakenings were the most frequent problem, with 44% of the sample noting this disturbance. Another study of patients with breast cancer found that 61% reported significant decrements in sleep quality (Fortner, Stepanski, Wang, Kasprowicz, & Durrence, 2002). Overall, patients with breast cancer report sleep disturbance that is approximately twice that of the general population (Savard, Laroche, Simard, Ivers, & Morin, 2003).

Distress related to the diagnosis of breast cancer has been identified as a likely contributor to the development of sleep disturbance (Roscoe et al., 2007). Specifically, depression predicted subsequent worsening of sleep disturbance in patients with breast cancer. Because sleep disturbance is a symptom of depression, this item was excluded

from analysis, with no alteration to the observed results (Palesh et al., 2007). Even after completing treatment for breast cancer, these women continue to report elevated sleep disturbance (Couzi, Helzlsouer, & Fetting, 1995). Evidence suggests that sleep disturbance is predictive of decreased subsequent quality of life in patients with breast cancer (Fortner et al., 2002). Based on these observations, a recent review has called for interventions specifically designed to reduce sleep disturbance in patients with cancer (Berger et al., 2005).

Not surprisingly, sleep disruption and disruption of circadian cortisol rhythms appear to affect one another (Koopman et al., 2002; Van Cauter, Leproult, & Kupfer, 1996), though not in all studies (Mormont et al., 2000). Circadian rhythmicity is essential to sleep functioning. This rhythmicity is largely generated by the suprachiasmatic nuclei (SCN) in the hypothalamus and affects both cortisol rhythms and sleep. The SCN circadian disruption is a recognized cause of sleep difficulty. The American Academy of Sleep Medicine describes eight groups of sleeping disorders, with one group being circadian rhythm sleep disorders. These include sleep disturbance resulting from alterations to the circadian timing system (American Academy of Sleep Medicine, 2005). Perhaps due to the availability of energy produced by elevated cortisol, elevated cortisol during the night is related to sleep disturbance (Van Cauter et al., 1996). Decreased sleep has been associated with higher cortisol levels in the evening (Koopman et al., 2002), a time when cortisol is typically approaching its nadir. Elevated evening cortisol values have been observed in women with breast cancer, and elevated evening cortisol is consistent with the flattened cortisol profile characteristic of women with breast cancer (Spiegel, Giese-Davis, Taylor, & Kraemer, 2006). Cortisol increases are also associated

with nighttime awakenings and increased stage 1 sleep, which is lighter and less restorative sleep, throughout the night (Born et al., 1986; Follenius, Brandenberger, Bandesapt, Libert, & Ehrhart, 1992).

Just as elevated cortisol, especially in the evening when cortisol is typically at its nadir value, is associated with sleep difficulty the following night, disruptions in sleep are associated with altered cortisol during the subsequent day. In patients with breast cancer, increased nocturnal awakenings have been associated with a flatter diurnal cortisol slope (Sephton, Sapolsky, Kraemer, & Spiegel, 2000). In a study of healthy adult men, the day following sleep deprivation was marked by increased total cortisol and delayed decrease of cortisol after the morning peak, suggesting that sleep disturbance could reduce the resiliency of the stress response system (Leproult, Copinschi, Buxton, & Van Cauter, 1997). Awakenings also appear to be related to increased nocturnal cortisol levels (Spath-Schwalbe, Gofferje, Kern, Born, & Fehm, 1991).

Actigraphy

In addition to endocrine circadian rhythms, the circadian activity rhythm, or sleep/wake rhythm, has been a variable of interest in patients with cancer. Actigraphy, or the recording of body movement, measures circadian rest-activity rhythms, or waking and sleep activity (Ancoli-Isreal et al., 2003). Polysomnography is typically considered the preferred method of distinguishing sleep from wakefulness. While sleep/wake indentification is similar, actigraphy does present several advantages over polysomnography. Using actigraphy to assess circadian rest-activity rhythms provides an unobtrusive measure of circadian rhythms and sleep-wake cycles (Ancoli-Isreal et al.,

2003). Once they are initialized, watchlike devices worn on the nondominant wrist record activity levels throughout the day and night without any need for maintenance. The unobtrusive nature of actigraphic assessments allows for naturalistic observation of sleep. Actigraphy also allows for long-term observation of circadian rhythms throughout 24 hours and across multiple days.

The rest-activity circadian cycle has been used as a reference for chemotherapy administration at specific times to improve tolerability and efficacy (Mormont & Levi, 2003). This measure has demonstrated prognostic survival value in a study of patients with metastatic colorectal cancer in which cortisol rhythms did not exhibit prognostic value (Mormont et al., 2000), supporting the use of multiple measures of circadian function. Actigraphic recordings correlate well with results obtained by traditional polysomnography, with correlations for total sleep overnight typically at or above .85 (Acebo & LeBourgeois, 2006). Actigraphy also correlates well with measurements of melatonin and core body temperature rhythms (Ancoli-Isreal et al., 2003; Selmaoui & Touitou, 2003). The usefulness of actigraphy in assessing activity rhythms is supported by the difficulty inherent in self-reported activity levels. Subtle changes in activity levels may be challenging to remember and accurately report. Also, self-reported sleep disturbances are sometimes not found when assessed with actigraphy (Dagan, Zinger, & Lavie, 1997).

Actigraphy has proven particularly useful as a tool for investigating quality of life and clinical features of breast cancer. Given the disruption of circadian physiology observed in cortisol rhythms in patients with breast cancer, it is not surprising that these women have also reported marked sleep disturbance in a sample of patients studied prior

to the initiation of chemotherapy (Ancoli-Israel et al., 2006). In women with breast cancer, actigraphy yielded unique data when compared with sleep diaries in one study. A sample of women with breast cancer who were participating in a sleep intervention reported fewer awakenings and less total rest in sleep diaries when compared with actigraphic recordings (Berger et al., 2002). In addition, nighttime awakenings noted by actigraphic recordings were observed to be related to increased fatigue following chemotherapy (Berger, et al., 2002).

In a study of circadian rhythms and cancer progression, Mormont et al. (2000) carried out a study using actigraphy as a measure of circadian rhythms in a sample of patients with metastatic colorectal cancer referred for chronomodulated chemotherapy. Actigraphic recordings and serum samples used to calculate circadian rhythms were collected prior to the initiation of chemotherapy. Actigraphy data yielded an autocorrelation as a measure of circadian rhythmicity and a variable that quantified the amount of motion while in bed as a measure of rest-activity rhythm. The rest-activity measure was related to tumor progression and survival in this study (Mormont, et al., 2000), lending support to the idea that sleep disturbance is of prognostic significance in patients with cancer.

The studies reviewed above indicate that actigraphy provides an unobtrusive, naturalistic estimate of sleep that is comparable to polysomnography, the gold standard for sleep assessment. Research indicates that actigraphy provides an objective measure yielding data not available from sleep diaries. In patients with colorectal cancer, the 24-hour rest-activity rhythm was predictive of tumor progression and survival, supporting the clinical importance of actigraphy in patients with cancer. However, the explanation

for disrupted circadian actigraphy rhythms is unclear. Further research is needed to determine whether psychosocial factors may influence disrupted circadian actigraphy rhythms. Investigation of psychosocial factors that may be related to circadian activity rhythms, a prognostic variable of interest in this population, may specify psychosocial variables or symptoms that merit close monitoring during the course of treatment. Monitoring of these symptoms may assist in identification of patients most likely to benefit from intervention. This research may also inform the structure and content of future interventions by identifying psychological symptomatology that may be related to disruption in circadian actigraphy rhythms. The relationship between psychological symptoms and actigraphy rhythms are particularly interesting because actigraphy rhythms are essentially a behavioral variable that may be amenable to influence by the patient. Although actigraphy has demonstrated relationships with melatonin and body temperature rhythms, the relationship between actigraphy and cortisol rhythms is not established and is of interest in this study.

Hypotheses

Figure 3 illustrates the proposed relationships between cancer-related intrusions, coping, and circadian disruption in this study. It was hypothesized that cancer-related intrusive thoughts would disrupt rhythms of both salivary cortisol and rest-activity rhythm as measured with actigraphy. The extent to which cancer-related intrusions disrupt circadian rhythms was hypothesized to vary as a function of the level of avoidant coping used. Specifically, it was hypothesized that increased avoidant coping would be associated with a stronger positive relationship between cancer-related intrusions and

circadian disruption. Finally, it was hypothesized that cortisol and rest/activity rhythms would be associated.

Figure 3. Hypothesized relationships between cancer-related intrusions, avoidant coping, and circadian disruption

Hypothesis 1a: Cancer-related intrusions will be significantly and positively associated with circadian disruption, as measured by salivary cortisol and actigraphy.

Hypothesis 1b: Avoidant coping will moderate the relationship between cancer-related intrusions and circadian disruption.

Hypothesis 2: Diurnal salivary cortisol slope and rest-activity rhythm obtained by actigraphy will be significantly and positively associated.

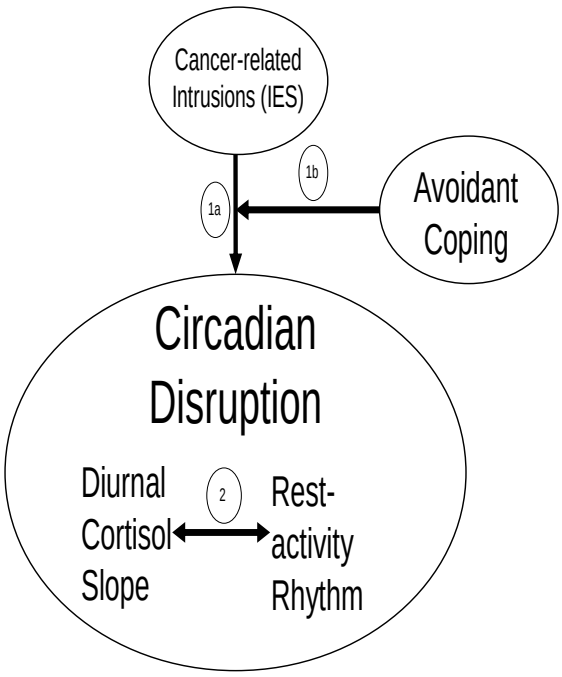


Figure 3. Possible relationships between cancer-related intrusions, avoidant coping, and circadian disruption.

Hypothesis 1a: Cancer-related intrusions will be significantly and positively associated with circadian disruption, as measured by salivary cortisol and actigraphy.

Cancer-related intrusions are of particular interest in women that have recently been informed of their diagnosis of breast cancer because of the potentially traumatic effect of the diagnosis (Andrykowski, Cordova, Studts, & Miller, 1998) and the subsyndromal PTSD symptoms often observed following diagnosis (Butler, Koopman, Classen, & Spiegel, 1999). A finding in breast cancer patients that cancer-related intrusions are associated with circadian disruption would support research suggesting circadian disruption as a mechanism for the effect of psychological distress on health by investigating whether a relationship exists between distress and the proposed mechanism, circadian disruption. Limited studies of the effects of intrusions on cortisol exist. In people living close to the damaged Three Mile Island nuclear power station, intrusions were associated with increased 15-hour overnight urinary cortisol (Davidson & Baum, 1986). In addition, intrusions have been related to increased plasma cortisol levels in homosexual males receiving HIV testing (Antoni et al., 1990). These studies examined alterations in cortisol production, but they did not include a description of circadian cortisol rhythms. This suggests that cortisol is responsive to intrusions following a specific event. Clearly, though, further research is needed to clarify this relationship.

Hypothesis 1b: Avoidant coping will moderate the relationship between cancer-related intrusive thoughts and circadian disruption.

Exploring the moderation of these relationships by coping will inform debate about possible psychological intervention. Participants in cognitive-behavioral interventions have demonstrated reduced cortisol in comparison to a wait-list control group (Cruess et al., 2000; Gruber et al. 1993), suggesting that active engagement of the stressor may influence the effect of the stressor on clinical outcomes. Undergoing psychosocial treatment typically includes engagement of the stressor through direct discussion of the experience of having breast cancer and learning coping skills aimed at ameliorating the effects of illness. Active coping efforts are in contrast to avoidant coping strategies that might otherwise be ineffectively used to manage intrusions.

Horowitz's (1976) view on stress response patterns was that initial intrusive thoughts are followed by avoidance that impairs adaptation to a traumatic experience. In addition to delayed processing of a negative event, avoidance could impair adaptation by preventing the implementation of other coping strategies (Jim, Richardson, Golden-Kreutz, & Andersen, 2006). Given the life-threatening nature of a diagnosis of breast cancer, it is expected that cancer-related intrusions will be prominent immediately after being informed of the diagnosis. However, avoidant coping is hypothesized to influence the effects of cancer-related intrusive thoughts on circadian disruption. When avoidant coping is low, intrusions may be part of adaptation to the stressor. It has been proposed that this adaptation is marked by the expression of catabolic hormones such as cortisol that are balanced by the expression of anabolic hormones that promote recovery from acute stressors and growth (Epel & McEwen, 1998). In this way, patients that are low in avoidant coping may not experience disruption of circadian rhythms related to intrusions. Rather, they may engage in emotional processing, which can promote meaning-making

and reduced distress (Kennedy-Moore & Watson, 2001). Conversely, intrusions related to a diagnosis of breast cancer may be related to circadian disruption in patients that inhibit processing by engaging in avoidant coping.

Research into avoidant coping as a moderator of the effects of breast cancer-specific intrusions on circadian disruption is lacking. As a result, the influence of avoidant coping on this relationship is unknown. Based on available research, it seems likely that avoidant coping will aggravate the effects of intrusions on circadian disruption, but the opposite relationship is possible. The patients in this study had learned of their diagnosis of breast cancer within the past few weeks. It is possible that avoidant coping could shield the patient from circadian disruption for a short period of time. If this is the case, elevated avoidant coping would be expected to be related to decreased circadian disruption, and decreased avoidant coping would exhibit an association with increased circadian disruption. In addition, it should be noted that direct effects of avoidant coping on psychological and physiological adaptation have also been researched. This is an interesting relationship because avoidant coping may have deleterious effects on circadian disruption regardless of the distress caused by a stressor such as breast cancer. It is possible that avoidant coping brings about a state in which individuals do not cognitively process a stressor and consequently are continually confronted by it (Park & Folkman, 1997). Due to the exploratory nature of this study, all possibilities will be considered.

Hypothesis 2: Diurnal salivary cortisol slope and rest-activity rhythm obtained by actigraphy will be significantly and positively associated.

Cortisol rhythms assessed using salivary samples and rest-activity rhythms assessed using actigraphy are both used as measurements of circadian disruption. The nature of these variables suggests they are related. The relationship between cortisol and rest-activity rhythms will be explored to investigate their effects on one another and the necessity of using both assessment methods in studies of circadian disruption.

METHOD

Participants

Because the transactional model is process oriented, it focuses on an individual's response to a specific stressor (Folkman, Lazarus, Dunkel-Schetter, DeLongis, & Gruen, 1986). In this study, the stressor (breast cancer diagnosis), setting (outpatient clinic), and timing (between diagnosis and initiation of treatment) were relatively consistent. The experience of having breast cancer is likely to vary considerably over time (Lazarus & Folkman, 1984, p. 146). Women often acquire information regarding cancer and its treatment that changes their understanding of the stressor. The rigors of treatment could worsen intrusions, or treatment could provide some relief in that efforts are being undertaken to address the illness and perhaps send the cancer into remission. Once treatment is initiated, the prognosis could improve or worsen depending on the cancer's response to treatment.

To attempt to control for variance in the stressor and timing, women with breast cancer that had been recently diagnosed were recruited between the time of diagnosis and the initiation of treatment. Because women with the same chronic illness (breast cancer) at the same body site (breast) make up this study, all of the participants share this stressor in common. By keeping the timing of diagnosis and treatment relatively consistent, variance in breast cancer as a stressor is reduced. In their presentation of the transactional model of stress and coping, Lazarus and Folkman (1984) argued against the

conceptualization of dominant coping responses that are employed across time andsituations. Rather, the investigation of coping efforts undertaken in response to a given type of psychological stress and at a certain time was identified as a topic in need of research.

Recruitment Procedure

Although study amendments modified the protocol during the accrual period, all participants in this study were women diagnosed with breast cancer who enrolled and completed data collection between the time of diagnosis and the initiation of treatment. Patients who were initially eligible for this study included newly diagnosed women referred for surgical treatment of breast cancer who spoke and read English proficiently enough to adequately complete questionnaires. The first participant was enrolled on 6/3/05. Nine patients were enrolled prior to the approval of an amendment on 1/31/06 that sought to eliminate variance in disease characteristics by restricting enrollment to patients with primary breast cancer. One additional patient was enrolled under this protocol before inclusion criteria were widened, due to accrual rate concerns, to all patients with stage I-IV (primary, metastatic, or recurrent) breast cancer on 3/17/06. Fourteen patients were enrolled under this protocol. To allow for secondary hypothesis testing, an amendment adding the collection of nipple aspirate fluid from the surgical procedure, when available, was approved on 10/27/06, and 20 patients were enrolled under this protocol. The final protocol stated that women diagnosed with stage I-IV (primary, recurrent, or metastatic) breast cancer who had not begun curative treatment such as lumpectomy, mastectomy, chemotherapy, or radiation and spoke and read English proficiently enough to adequately complete questionnaires would be eligible for the study.

Patients who were referred for surgical consultation were informed of the results of their biopsy, an examination of breast tissue by a pathologist to determine whether a malignancy is present. There are four types of breast tumor biopsy. A core biopsy uses a hollow needle to remove tissue from an area of the breast suspected of being cancerous. A fine needle aspiration uses a thinner needle to remove cell samples from an area of the breast suspicious for cancer. An excisional biopsy surgically removes suspicious tissue from the breast as well as some healthy tissue in the surrounding area. An incisional biopsy surgically removes a portion of the suspicious tissue from the breast. A vacuum-assisted biopsy uses a needle to take multiple samples from the suspicious area of the breast with one needle insertion.

Patients referred for this study had been diagnosed in several different ways. Some patients referred for this study had received feedback regarding biopsy results during the visit that immediately preceded their invitation to enroll in this study. However, some patients received biopsy information from another physician prior to being referred for surgical consult. In addition, some patients were informed of pathology results indicating a diagnosis of breast cancer over the phone prior to their surgical consult visit. Finally, it should be noted that some patients were told that they likely had breast cancer based on preliminary testing, prior to undergoing the pathology testing necessary for a definitive diagnosis. As a result, most patients reported they had learned of their breast cancer diagnosis prior to the date of their clinic visit and enrollment in this study. These patients completed testing needed to confirm a diagnosis of breast cancer before being referred to this study, which accounts for the time lag between self-reported diagnosis date and referral to this study. At the conclusion of their clinic visit, eligible patients were

introduced to the study by the surgeon, and then met with a research assistant to receive information about the study and an invitation to enroll.

Because chart reviews did not reveal the precise time of diagnosis, the time lag between diagnosis and enrollment in this study was calculated as the number of days between each participant's reported date of diagnosis and the day the first daily questionnaire was completed. Because participants were asked to complete the first daily questionnaire one day after enrollment into the study, one day was subtracted from the difference between diagnosis date and the first day of data collection. Four participants did not provide a diagnosis date, so the earliest reference to a diagnosis of breast cancer available in the medical chart was used for these participants. The time between diagnosis and enrollment ranged from 0 to 122 days, with a mean of 17.8 days (SD = 21.2) and median of 14 days.

All of these patients completed data collection prior to undergoing surgical treatment for breast cancer. Surgeries typically occurred approximately four weeks after patients were informed of the diagnosis of breast cancer. Figure 4 demonstrates the timeline for patient treatment and recruitment into the study. Patients diagnosed with ductal carcinoma in situ (DCIS), cancerous cells that line the milk ducts but have not grown into the surrounding breast tissue, were not targeted for this study because study materials discussed the diagnosis of breast cancer, and these patients had been informed that they had precancerous, as opposed to cancerous, cells. Patients with DCIS were not specifically excluded from the study in initial inclusion/exclusion criteria, and one patient with DCIS was enrolled based on referral for breast cancer, but later pathology results indicated this patient had DCIS, as opposed to invasive breast cancer. Because patients

with DCIS confronted the option of surgery and previous research has indicated a significant psychological impact of DCIS on patients (DeMorgan, S., Redman, S., White, K., Cakir, B., & Boyages, 2002), the three patients with DCIS who were enrolled were included in analyses.

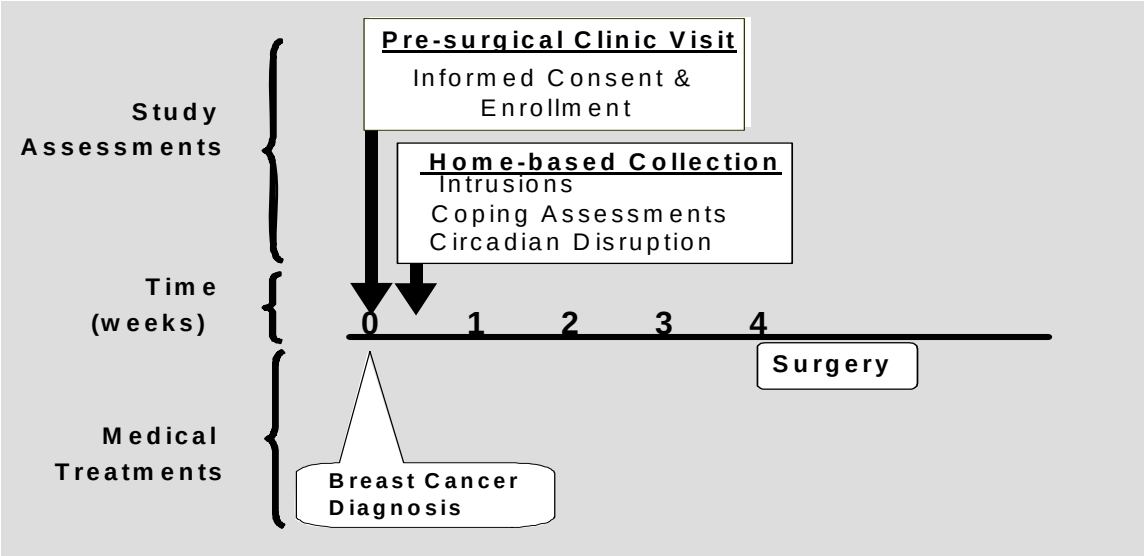


Figure 4. Study assessments with respect to the expected timeline of medical treatments. At the "Pre-surgical Clinic Visit", patients met their surgeon regarding breast cancer diagnosis, then enrolled in the study and were given materials for home-based data collection. All data collection was completed prior to surgery. After completion of four days of "Home-based Collection", patients returned study materials to the investigator. Home visits were arranged as needed.

Patients were recruited at the Brown Cancer Center, Norton Healthcare Pavilion and Children's Foundation Building by referral from surgeons Dr. Anees Chagpar and Dr. Kelly McMasters. Medical charts were reviewed at the outset of the clinic day to screen for potentially eligible patients. Because a confirmed diagnosis of primary breast cancer was required for inclusion, the surgeons determined patient eligibility during the clinic visit. Eligible patients that were not referred to the study due to demands on clinical time, patient unavailability due to scheduled events that did not allow for interview with

research staff, or research staff unavailability due to being occupied with other patients were identified by speaking with medical staff at the end of the clinic day. These patients were contacted by phone and invited to participate in the study. Three of the twelve patients approached in this manner were enrolled and provided enough data to be included in analyses. After the surgeon had introduced the study, a research assistant met with the patient at the clinic, provided information about the study, and answered any of the patient's questions. All participants recruited for participation in the study were asked to sign informed consent and HIPAA Research Authorization protocols approved by the University of Louisville Institutional Review Board on the use of human subjects in research.

Participants were given two questionnaire packets, a saliva collection kit, and an actigraphy device. A research assistant explained the rationale and procedure for filling out daily questionnaires assessing the previous day's intrusions, coping, and data collection each morning. The research assistant also explained saliva collection using collection materials, and participants were invited to practice using these materials.

Patients who met eligibility criteria for this study were initially recruited by phone after a call from the clinic to a research assistant following the patient's appointment with the surgeon. Due to poor accrual early in the study, graduate research assistants were given space behind the nursing desk to monitor patient flow and ensure that patients were referred to the study. Research assistants actively worked together with clinic staff to build relationships, discuss issues or problems, and encourage referrals.

Seventy-four potentially eligible patients were referred for this study between May 2005 and June 2007. Five patients referred after leaving the clinic because of

patients' time demands were unable to be contacted by phone. Of the 18 patients who declined to participate, 15 declined due to time constraints and/or response burden, two did not specify a reason, and one stated she was uncomfortable consenting to chart reviews. Seven patients enrolled in the study but were unable to provide enough data to be included in any primary analyses. Of these seven patients, one patient provided no data due to acute illness and another patient provided no data due to the time demands of attending to visiting family. Two patients provided complete data except for rest/activity rhythms due to technical problems with the actigraphy device and were not included in analyses with actigraphy variables, but data provided by these two patients were part of analyses with no actigraphy variables, including analyses for hypotheses 1a and 1b with cortisol as an outcome variable. Similarly, one patient provided complete data except for saliva samples, so she was eligible for analyses testing effects on actigraphy outcomes for hypotheses 1a, 1b, and 2, but not in analyses testing effects on cortisol outcomes. One patient was excluded from all analyses with cortisol variables because she reported taking systemic steroids, which alter salivary cortisol. The remaining patients who provided incomplete data did not provide questionnaire data sufficient for analysis, with one of these patients also missing the majority of the saliva samples requested in the study protocol. Forty-five patients provided enough data to be included in analyses.

Daily Assessments of Intrusions and Avoidant Coping

Daily self-reports of breast cancer-specific intrusions and avoidant coping were collected to assess coping efforts employed in a given day, as opposed to trait-oriented measures that ask participants to recall which coping strategies they usually employ. A

drawback of trait-oriented measures of coping is that, even if a participant has a dominant coping response, it may not be used in response to a given stressor at a given time. In contrast, questionnaires used in this study asked about the participant's coping efforts that occurred over the course of one day in response to the experience of having breast cancer. The data obtained by daily assessments aim to minimize the influence of the daily variability in intrusions and coping on the assessments obtained.

Daily assessments also present an opportunity to reduce retrospective reporting bias by placing the time of the assessment close to the time of the event of interest. Recall of breast cancer-specific intrusions and avoidant coping that occurred yesterday is likely to be better than recall of coping efforts that occurred a longer period of time prior to the assessment. Previous studies suggest that retrospective report bias alters recollection, and that daily assessments provide different data than retrospective reports relying on memory to assess events occurring farther from the time of assessment (Erskine, Morley, & Pearce, 1990; Larsen, 1992; Margraf, Taylor, Ehlers, Roth, & Agras, 1987; Rapee, Craske, & Barlow, 1990). Also, the transactional model of stress and coping used to inform the design of this study is dynamic, with coping efforts and outcomes continually altering one another and the stressor. These alterations magnify the retrospective reporting bias for the topic of research. An assessment at the outset of the collection period would sample only a small portion of the data available over that time span. Conversely, an assessment at the end of the collection period would likely prompt participants to describe their coping based on heuristics, personal beliefs about the stress, coping and adaptation process, or salient events (Tennen & Affleck, 2000). As a result, daily assessments provide a means of collecting data over the entire study period while

minimizing problems associated with retrospective reporting of these phenomena. Overall, the use of daily assessments in this study adheres more faithfully to the transactional model of stress and coping by assessing coping as an effort undertaken within a specific context, as opposed to assessing a coping strategy as it applies broadly to all contexts. Daily assessments reduced retrospective reporting bias by asking participants to report on a brief period of time, one day, that occurred recently.

Participants were asked to complete daily assessments each morning, as opposed to completing them immediately before going to sleep, to minimize the effect of the assessments on sleep. Intrusions, in particular, are of concern because pre-sleep intrusions are likely to be related to sleep disturbance (Gross & Borkovec, 1982; Wicklow & Espie, 2000). While investigation of this relationship is one focus of the study, an influence of study methodology would limit the generalizability of any knowledge obtained by this study. If participants were prompted by questionnaires on breast cancer-specific intrusions and avoidant coping to think about breast cancer immediately prior to going to bed for the night, findings regarding a relationship between intrusions and circadian disruption may not apply to most patients with breast cancer, who are not typically prompted to think about breast cancer-specific intrusions prior to going to bed. Pre-sleep assessments could also disrupt participants' bedtime routines by including an extra activity. To the extent that this disruption would alter participants' sleep, the disruption of bedtime routines would further compromise the validity of the circadian rhythmicity data obtained.

Physiological Data Collection

Circadian Disruption

Salivary Cortisol - Cortisol has a strong circadian rhythm that is measurable in saliva, and it is an important messenger in the circadian control of peripheral tissues by the central clock (Mormont & Levi 1997). Salivary cortisol provides a reliable estimate of free hormone levels in blood (Kirschbaum & Hellhammer, 1994). Salivary cortisol was measured in a series of twelve saliva samples collected by participants at home over 72 hours. At the time of enrollment a study coordinator met with the patient to explain saliva collection procedures, demonstrate the use of study materials, and allow the patient to practice using these materials. Written instructions for saliva sample collection is provided in Appendix A. Participants were given multiple phone numbers of study coordinators and encouraged to call with any questions about the study or data collection.

Participants received twelve pre-labeled "salivette" tubes (Walter Sarstedt Inc., Newton, North Carolina). Collection was requested for three consecutive days at waking, 30 minutes after waking (+30 min), at 4 p.m., and just before going to bed. The sampling times were selected because they allow calculation of the diurnal cortisol slope, a variable that is prognostic for survival in metastatic breast cancer patients (Sephton et al., 2000). Medication Event Monitoring System (MEMS) bottles and caps (Aardex, Ltd.) were used to store cotton saliva collection swabs. MEMS caps contain microelectronics that record the exact time and the date the bottle is opened, and a software program stores collection time data. An interface was used to download Medication Event Monitoring System (MEMS; Aardex, 2001) data on times of saliva sample completion onto computer after these devices had been used to assess the times at which participants had removed cotton

swabs to provide saliva samples.

Participants were asked not to eat, drink, brush teeth, use mouthwash, chew gum, or smoke for the 30 minutes prior to saliva sample collection. The purpose of the MEMS devices in recording sample collection times was explained to participants, and they were asked to open the MEMS devices only when providing a saliva sample and to close the lid tightly when done using the device. Participants were instructed to also record sample collection times on stickers placed on the salivettes with a marker provided in the collection kits. Participants were asked to refrigerate samples as soon as possible after collection but informed that it was permissible to leave samples unrefrigerated if necessary, such as a 4pm sample provided while at work. They were advised that samples could not be left unrefrigerated for more than a day.

Cortisol assays were conducted by Elizabeth Lush and Robyn McLean at the Biobehavioral Research Laboratory at the University of Louisville. A research assistant centrifuged, aliquoted, and froze saliva samples at -80 °C. Assays were conducted using an enzyme immunoassay (EIA) developed for use in saliva (Salimetrics, Inc., State College, PA). The sensitivity of the assay was 0.007 ug/dL. The inter-assay coefficient of variation was 7.4% using the low control and 3.4% using the high control. The intra-assay coefficient of variation was 5.7% using the low control and 2.8% using the high control. Because cortisol values are typically positively skewed, cortisol values were log-transformed prior to analysis for all primary cortisol outcomes. Calculated variables were the diurnal mean (mean of all 12 log-transformed values), diurnal slope (unstandardized beta weight of natural log-transformed cortisol regressed on collection time excluding +30min sample), mean waking level, and cortisol awakening response (CAR) slope,

calculated by regressing the unstandardized beta of the wake and +30min log-tranformed cortisol values on the collection times, and mean bedtime cortisol. The wake cortisol value was chosen as the first value for the calculation of the diurnal cortisol slope to reduce collinearity with the CAR slope and because using the waking value to anchor the calculation of the diurnal slope has been shown to promote more reliable calculation across days (Kraemer et al., 2006). The CAR slope was chosen as the primary measure of the HPA response to awakening because the CAR % increase and area under the awakening curve are more influenced by the level of the awakening cortisol value and consequently were not considered as valid an index of the response to awakening as the CAR slope.

For secondary analysis, CAR % increase was calculated using the mean percent increase from the wake to the +30min raw cortisol values, and the area under the awakening cortisol curve was calculated using log-transformed cortisol values for the wake and +30min samples. The area under the awakening cortisol curve was calculated using log-transformed cortisol values because the raw values did not have a normal distribution. A questionnaire was used to query sample collection times as well as factors that may affect cortisol secretion, such as medications, stressors, sleep, exercise, and menstrual cycle phase.

Actigraphy

Actigraphy, or the recording of body movement, measures circadian rest-activity rhythms, or waking and sleep activity. Body movements were recorded by a device called the Mini-Motionlogger (Ambulatory Monitoring Systems, Inc., Ardsley, NY 10502), and

stored for later analysis. An interface was used to transfer data from actigraphy devices onto computer (Ambulatory Monitoring, 2004) after participants had worn the device on their wrists for three consecutive days. These devices were worn on participants' wrists where a piezoelectric beam generated voltage each time the device moved. Data were quantified using the proportional integration mode of the Mini-Motionlogger. This mode performed better than other modes when comparing scores to polysomnography (Jean-Louis, 2001). Motions were recorded in 60-second segments, with voltage signals from each minute creating a curve, allowing for calculation of area under the curve (AUC). A moving average AUC is calculated for seven-minute segments that include the previous four and subsequent two minutes. Segments are scored as "wake" or "sleep" using calculations based on the University of California – San Diego (UCSD) Sleep Scoring Algorithm (Cole, Kripke, Gruen, Mullaney, & Gillin, 1992).

The circadian rhythm in activity was estimated using the autocorrelation coefficient calculated based on 24-hour time lags. This autocorrelation assesses the association of data in a given 1-minute time period with data in that same 1-minute time period on other days. Dowse and Ringo (1989) described the autocorrelation calculation as follows: "If X_i is the measurement at time i, the correlation coefficient rk, between X_i and X_i+k is computed for lags k, with k = 1 to 4320 minutes (72 hours)". Briefly, the autocorrelation is a measure of circadian consistency, the similarity of rest/activity patterns across days (Roscoe et al., 2002). Using this calculation, a higher autocorrelation is indicative of a more pronounced circadian rhythm. Participants with a strong circadian rhythm would be expected to exhibit similar activity levels at similar times of day, yielding a high autocorrelation. Circadian rhythmicity was also assessed using two

dichotomy indices. The dichotomy index for time in bed yields the percentage of time spent in bed in which the activity level falls below the median activity level for time out of bed. Conversely, the dichotomy index for time out of bed yields the percentage of time spent out of bed in which the activity level falls below the median activity level for time in bed. In both cases, a higher dichotomy index indicates more frequent inactivity, but inactivity while in bed is consistent with strong circadian rhythmicity, while inactivity while out of bed is consistent with circadian disruption. Sleep variables yielded by actigraphy data included sleep latency, total sleep time, sleep efficiency (% of time in bed that the participant is asleep), and awakenings. Someone with a strong circadian rhythm would be expected to exhibit high dichotomy index percentages for time in bed and low dichotomy index percentages for time out of bed. Table 1 presents circadian rhythm variables, calculation methods, and implications.

Table 1. Circadian rhythm variables, their methods of calculation, and descriptions of their meanings. All cortisol values measured in (μg/dL).

Actigraphy		
Variable	**Calculation**	**What it Means**
Autocorrelation	Correlation of 1-minute epoch on one day with same epoch on different days	Lower value indicates disrupted circadian activity rhythm
Dichotomy/Inside (D/I)	% of time in bed in which activity falls below median activity for time out of bed	Lower value indicates more activity while in bed (circadian disruption)
Dichotomy/Outside (D/O)	% of time out of bed in which activity falls below median activity for time in bed	Lower value indicates less activity while out of bed (circadian disruption)
Cortisol		
Waking Cortisol	Mean natural log-transformed cortisol value across all saliva collection days	Cortisol level immediately after first waking

Variable	Calculation	What it Means
Morning Slope	Waking and +30min natural log-transformed cortisol regressed on collection times	Primary measure of CAR, higher values indicate greater HPA activation in response to awakening
CAR % increase	Mean % increase from waking to +30min using raw cortisol	Secondary measure of CAR, higher values indicate greater HPA activation in response to awakening
Area Under the Awakening Cortisol Curve	Total area under slope from mean waking to mean +30min using raw cortisol values, then total was natural log-transformed	Secondary measure of CAR, higher values indicate greater HPA activation in response to awakening
Diurnal Cortisol Slope	Waking, 4pm, and bedtime natural log-transformed cortisol regressed on collection times	Higher values indicate abnormal rhythms that can include low morning level, peaks occurring in the afternoon or evening, or flattened rhythms
Overall Diurnal Mean Cortisol	Mean of all natural log-transformed cortisol samples	Total cortisol secretion
Bedtime Cortisol	Mean of all natural log-transformed bedtime cortisol samples	Cortisol levels at bedtime

Blood Pressure and Heart Rate

Patients presenting at the surgical clinic typically underwent assessments of blood pressure and heart rate that were available in the patient's medical record. Chart review sought to obtain these data. When more than one assessment was available in the patient's medical record, the assessment closest to the time of study enrollment was recorded in the study database.

Data Storage and Management

Data were retrieved by coordinating with patient hospital visits, arranging to meet at the patient's treatment center, or a research assistant driving to the patient's house. Questionnaires were reviewed to ensure completeness, and patients were asked to complete items that they missed, though they retained the option to decline to answer these items.

Assessments

Potential control variables

Participants completed a brief background questionnaire assessing demographics such as age at diagnosis, ethnicity, marital status, religious affiliation, family size, education, employment, household income, medical history, and current medications. All ages were calculated based on the most recent diagnosis, as opposed to the time of the first cancer diagnosis in cases of recurrent cancer.

The participants' medication regimens were assessed on the day of study enrollment as part of the initial interview. Each participant was prompted to report the medication, dosage, number of times per day or week it was taken, and the reason it was taken. Medications were then entered the database according to their medication class. In the database, the first column listed the total number of medications from a given class the participant reported taking. The next column presented the generic name of the specific medication taken. If multiple medications from one class were part of the participant's medical regimen, a third column listed all of them.

Systemic steroids were separated from other steroids (e.g. nasal steroids) in the database because systemic steroids are known to affect cortisol assessments. Oral, patch, and vaginal ring contraceptive medication were recorded as systemic contraceptives, separately from other forms of contraception because systemic contraceptives likely alter cortisol levels. One participant was excluded from analyses involving cortisol summary variables due to reporting use of oral fluticasone A sleep variable was created that included all medications patients reported taking for the purpose of sleep because circadian rhythms and sleep were a focus of this study. Medications were included in this category even if they belonged to another medication class. Finally, antidepressants were among the classes of drugs recorded in the database, as they likely influence cortisol levels.

Data on disease status (diagnostic testing, age at diagnosis, time since diagnosis, stage, grade, time since diagnosis, age at diagnosis) was collected by chart review. Reviews were conducted by study personnel Eric Dedert, Elizabeth Lush, and Meagan Martin in the medical records office at the Children's Foundation Building in Louisville, Kentucky. Reviews were conducted for all patients. A medical review form containing the variables listed above was used to standardize the variables sought in review.

Breast cancer-specific intrusions

Impact of Event Scale (IES) – The IES (Horowitz & Wilner, 1979) is a 15-item measure that was developed based on studies of responses to stressful events. In particular, intrusions and avoidance associated with the event are assessed. In this study, the event was specified as the diagnosis of breast cancer. Participants rate whether comments on

the scale are true for them “Not at all”, “rarely”, “sometimes”, or “often”. Scores are obtained by assigning the weights 0, 1, 3, and 5 to the frequency categories indicated. Participants rate how frequently these symptoms were true for them on a four-point scale. The IES has been utilized in several samples, including patients with breast cancer (Cordova et al., 1995). A review of psychometric properties of the IES reported high internal consistency indicated by a mean alpha reliability coefficient of 0.86 for the intrusions subscale (Sundin & Horowitz, 2002). A study with patients scheduled for breast biopsy reported reliability of .89 for the intrusions subscale and .85 for the avoidance subscale (Lebel et al., 2003). In the current study, Cronbach’s alpha was .930 for items collapsed across days, with alpha coefficients for individual days ranging between .856 on day one and .930 on day four,

The initial report on the IES noted a correlation of .41 between the two subscales, intrusion and avoidance, suggesting that these subscales are related but not redundant (Horowitz & Wilner, 1979). Studies have generally found moderate correlations between these two subscales (Sundin & Horowitz, 2002). Examination of convergent validity by comparing the IES with the Mississippi Scale for Civilian PTSD, an existing measure of reactions to a traumatic event, revealed that the two measures were moderately correlated ($r = .51$; Devilly, Spence, & Rapee, 1998).

The IES is particularly well suited to this study because breast cancer can be specified as the stressor, allowing for a more focused analysis of the intrusions related to being diagnosed with breast cancer. The original instructions prompt respondents to provide data on how frequently statements were true for them *during the past seven days*. To orient responses specifically to intrusions related to breast cancer in the past day, a

portion of the instructions for the daily questionnaire were modified to read "Please fill in each item, indicating how frequently the comments were true for you YESTERDAY regarding your diagnosis and treatment of BREAST CANCER". The 7-item intrusions subscale of the IES was completed upon awakening on four consecutive mornings and asked about the previous day's intrusions. All daily questionnaires were completed after participants had provided an awakening saliva sample. The awakening saliva sample was given priority because any delay in this sample would be likely to obscure the true awakening cortisol value due to the sharp increase in cortisol that typically occurs within minutes after awakening (see Appendix A for data collection instruction in "Daily Questionnaire"). The mean intrusions score from the four consecutive mornings was used in analyses.

The IES was initially conceptualized as a measure of intrusions and avoidance, but subsequent studies of the factor structure of this measure have argued for alternative conceptualizations. In addition to examining the intrusions and avoidance subscores, examination of the summary score of the entire IES has been proposed based on a study with Vietnam veterans (Hendrix, Jurich, & Schumm, 1994). A three-factor model, including a sleep disturbance scale as well as the traditional intrusions and avoidance subscales, has also been proposed (Larsson, 2000). Finally, a proposed four-factor model has added a numbing factor to those included in the three-factor model. This study found that four factors produced the best fit in a sample of police officers and fire fighters assessed eight years after they had been involved in rescue work at the site of an airplane crash (Witteveen et al., 2006). The sleep disturbance factor of the four-factor model was comprised of item 4 ("I had trouble falling asleep or staying asleep, because of pictures or

thoughts about it that came into my mind") and item 6 ("I had dreams about it"). The content of these two items supports an interpretation of them as indicators of sleep disturbance in addition to, or as opposed to, intrusions characterized by disturbing dreams. To determine whether the inclusion of these two items influences the relationship between intrusions and circadian disruption, secondary analyses were conducted with these two items removed.

Although the IES includes items assessing avoidance, these items were not included in the daily questionnaire. The IES avoidance items were also not used in analyses of avoidant coping because the IES conceptualizes and measures avoidance as a symptom of distress. (Horowitz, 1976). Consequently, the avoidance items from the IES are not appropriately conceptualized as avoidant coping, and a measure of avoidant coping efforts was used instead of the avoidance subscale of the IES. An attempt was made to keep the daily assessment procedures as brief as possible because participants were recruited at a site at which the research group had not previously recruited and were adjusting to a recent breast cancer diagnosis, and it was unclear what response burden might be most appropriate. In addition, there was concern that lengthy assessment procedures completed at a specific time of day might interfere with circadian rhythms. In addition, intrusions were a focus of this study because they are a measure of distress that was expected to be especially closely connected to the diagnosis of breast cancer.

Avoidant coping

Brief COPE – The Brief COPE is a 28-item self-report measure (Carver, 1997) that is an abbreviated version of the original 60-item COPE (Carver et al., 1989). Validation

studies of the COPE supported the 14 factor structure of the measure (Carver et al., 1989). The Brief COPE was developed because the author found that the original version had considerable redundancy and was found to be too lengthy by respondents (Carver, 1997). Subscales from the COPE were reduced to 2-item subscales for the Brief COPE in a study of residents recovering from a hurricane in their community. Items were chosen for inclusion in the Brief COPE based on high loadings with its factor in the original study and clarity based on feedback from prior studies (Carver, 1997). In the current study, the 'denial', 'self-distraction', and 'behavioral disengagement' subscales were used to derive the avoidant coping subscale score. In the original validation study, the alpha reliability coefficients for these scales were .54, .71, and .65, respectively (Carver, 1997). In validation studies for the original COPE, the 4-item subscales that ultimately became the 2-item denial, self-distraction, and behavioral disengagement subscales correlated negatively with optimism and perceived control, and positively with anxiety (Carver et al., 1989). Factor analysis has supported the use of the denial, self-distraction, and behavioral disengagement scales to comprise an avoidant coping scale (Rudnicki, Graham, Habboushe, & Ross, 2001). Avoidant coping was assessed in this study using the two items from self-distraction, denial, and behavioral disengagement on the Brief COPE, for a sum of six items.

The original development of the COPE had instructions that read "this questionnaire asks you to indicate what you generally do and feel when you experience stressful events". There was also a situational version that asked respondents to think about the most stressful event that had happened to them over the past two months and report on the coping they used in response to that event (Carver et al., 1989). For the

current study, the instructions were modified to read "This questionnaire asks you to indicate what you did and felt yesterday, when you experienced stressful events related to having breast cancer". The author has supported the adaptation of this measure to research applications through the alteration of the measure's instructions and verb tense of the items (Carver, 1997), and this has previously been done in studies of breast cancer patients' coping with breast cancer (Bellizzi & Blank, 2006). The Brief COPE has been used in studies of patients with breast cancer (David, Montgomery, & Bovbjerg, 2006; Fogel, 2004).

In the current study, the 6-item avoidant coping scale was completed on four consecutive mornings and asked about the previous day's avoidant coping. As with the IES, daily assessments of avoidant coping aimed to minimize measurement error due to retrospective reporting bias while increasing adherence to the transactional model of stress. Questionnaires were completed after participants had provided the awakening saliva sample. The avoidant coping score used for analyses was the mean avoidant coping score from the four collection times. The IES avoidance subscale was not included in daily assessments and not used in any analyses. Cronbach's alpha for the 6-item scale was .939 when items from all four days were assessed, with alpha reliability coefficients for individual days ranging from .710 for day four to .851 for day three.

Profile of mood states (POMS)

The POMS (McNair et al., 1971) is a 65-item scale assessing six dimensions of affect. It was designed to assess rapid fluctuations in mood and conceptualized moods as rapidly changing. The POMS has been used in a number of studies of patients with

cancer (Cassileth et al., 1985). The POMS was administered in a packet with other measures to be used for future analyses, to be completed at a time during the four day data collection period that was convenient for the participant. In contrast to the daily assessments, the POMS was completed only once during the course of data collection. In the current study, the depression-dejection subscale was used to identify participants that may be suffering from clinically significant depression in secondary data analysis (Patterson et al., 2006).

Data Reduction and Analysis

Control Variables

All questionnaire data were manually entered, cleaned, and examined for abnormal responses. Bivariate correlations were used to examine relationships of control measures with cortisol and actigraphy variables and evaluate these variables as potential candidates for inclusion in hierarchical regression equations. Age at diagnosis and summary stage were used as control variables in all analyses. Additional potential control variables included racial background education, income, weight, systolic blood pressure, diastolic blood pressure, tumor size, nodal involvement, estrogen receptor status at the time of diagnosis, progesterone receptor status at diagnosis, human epidermal growth factor receptor (her2/neu) status at diagnosis, tumor grade at diagnosis, time since diagnosis, each class of medications taken by at least 5% of the sample, and all medications taken for the purpose of sleep.

Approach to Primary Analyses

Data were analyzed using an exploratory approach, as opposed to a confirmatory approach. The aim of an exploratory approach is to maximize the depth of investigation, develop a better understanding of a dataset, and to generate hypotheses for future research. Consequently, no formal adjustments for multiple comparisons, such as a Bonferroni correction, were used in this study. The drawback to exploratory research is that statistically significant findings must be viewed with skepticism because a large volume of analyses is likely to yield some significant relationships that are spurious (Babyak, 2004). As a result, it is crucial to exploratory research to be cautious in interpreting the results obtained.

Exploratory analyses are useful for investigating relationships that are not yet well understood. Although significant research on breast cancer-specific intrusions and avoidant coping has taken place, the relationships between these variables and circadian physiological and rest/activity rhythms have not ever been studied. In addition, Lazarus (Lazarus, 2000) noted the limits of the search for causal variables in coping and adaptation research, and called for more detailed analyses of coping and adaptation aimed at developing a richer understanding of a process. He acknowledged that this research would likely need to proceed with smaller sample sizes and a less sophisticated understanding of causal variables. Nevertheless, he added that these more detailed studies would be as valuable as traditional studies of causal variables in contributing to research in coping and adaptation (Lazarus, 2000).

Preliminary Analytical Procedures

The assumption of normal distribution of variables was evaluated for all variables by examining boxplots and histograms. For variables that did not exhibit a normal distribution, Spearman correlations were used, as opposed to Pearson correlations. Exploratory bivariate correlations were calculated to allow for examination of relationships between potential control variables and circadian disruption variables.

Predictor Variables

The IES was initially conceptualized as a measure of intrusions and avoidance, but subsequent studies of the factor structure of this measure have argued for alternative conceptualizations. In particular a three-factor model with sleep disturbance supplementing the two traditional factors (Larsson, 2000) suggests a 5-item version of the intrusions scale is more appropriate. Due to conflicting conceptualizations of items four and six as indicators of intrusion (Horowitz, 1979) or sleep disturbance (Witteveen, 2006), separate calculations of intrusions scores were conducted. For all primary analyses, the traditional IES intrusions subscale was derived from a summary of the seven items on the intrusions scale of the IES (Horowitz, 1979). An alternative intrusion subscale was constructed with items four and six removed, and the remaining five items summed to yield a score that was used in secondary analyses only.

Actigraphy Data Reduction

Dr. Ehab Dayyat, a researcher with the University of Louisville, Department of Pediatrics who is experienced in scoring actigraphy data, was consulted to develop

competency in determining cutoff points for the beginning and ending of deleted data periods and in setting sleep onset and awakening times. Participants were asked to remove the actigraphy device only if they were participating in an activity that was likely to get the device wet. Device removals were recorded on the daily questionnaire (see Appendix A "Daily Questionnaire"). These reported removals were compared against actigraphy data to identify episodes to be deleted from actigraphy data files and excluded from calculation of outcome variables. Actigraphy files were also examined to identify extended periods of zero values that likely indicated actigraphy device removal to be deleted prior to outcome variable calculation.

Sleep intervals were set for each participant by integrating self-reported sleep onset and awakening times with actigraphy data. When the reported sleep interval was not concordant with the sleep interval indicated by the actigraphy data, preference was given to actigraphy data. The participant's typical level of activity during wake periods was compared with typical levels of activity during sleep to inform determinations of sleep onset and awakening. The sleep onset time was set at the first epoch in which a sustained period of time characteristic of the level of activity observed during sleep. The awakening time was set as the first epoch with a level of activity characteristic of waking levels that was followed by similar activity levels shortly afterward.

Actigraphy data were scored using the University of California San Diego (UCSD) Scoring Algorithm (G. Jean-Louis, Kripke, D., Mason, W., Elliott, J., Youngstedt, S., 2001) that was optimized using polysomnography as the criterion. Scoring of sleep/wake data was performed by the Action4 software (Ambulatory Monitoring, 2004).

To minimize an observed bias toward over-scoring wake in the UCSD algorithm (Cole, 1992), rescoring rules were developed by Webster, Kripke, Messin, Mullaney, and Wyborney (Webster, 1982) to improve accuracy of actigraphic sleep/wake estimates. However, data on more recent devices have revealed that these rescoring rules increased the sensitivity to wake of the algorithm but decreased the specificity of wake estimates, resulting in considerable bias. More importantly, Webster's rescoring rules did not improve the accuracy of the algorithm when compared to polysomnography (G. Jean-Louis, Kripke, D., Cole, R., Assmus, J., Langer, R., 2001). Consequently, Webster's rescoring rules were not used with the actigraphy data in this study.

Data Reduction

Reports from at least two of the four daily reports of intrusions or avoidance were necessary for inclusion in analyses involving one or both of these variables. Mean substitution was used to replace missing values if at least half of the items were completed for a given measure of subscale. For each participant, all daily assessment responses for a given measure were summed. This sum was then divided by the number of days for which data were available. The resulting dividend was the mean daily score for intrusions or avoidance across the assessment period. This dividend was used for all analyses.

Saliva sample collection times were available from MEMS devices that recorded openings. Participants also recorded the collection times on the salivettes while providing the sample. The MEMS and self-reported collection times correlated very highly (Spearman's r = .977), suggesting that participant reports of collection times were reliable

and comparable to other reports (Kraemer et al., 2006). Recent data argue the inclusion of MEMS caps may increase participant response burden without increasing protocol adherence (Kraemer et al., 2006). However, the possible response burden introduced by MEMS caps has already been incurred and data indicate it is possible that MEMS collection times are more reliable than self-reported collection times (Kirschbaum, 1994). As a result, MEMS collection times were given preference of self-reported collection times. Self-reported collection times were used when there was no MEMS time available, such as a series of two samples with a MEMS opening recorded for the first sample only. This was taken as an indication that the participant removed two cotton swabs during one opening (Kraemer et al., 2006) to increase the convenience of sample provision. In addition, no MEMS data were available for three participants due to device malfunctions. A total of 48 of an overall total of 528 saliva samples included in analyses used self-reported collection times because MEMS times were not available. Collection times that were more than four standard deviations from the mean time for a given sample period (awakening, +30min, 4pm, and bedtime) were identified as outliers and examined for any possible confounds by considering participant comments and actigraphy data. Collection time outliers were limited to one patient who did have cortisol time outliers and reported she worked third shift sometimes, including portions of the data collection period for this study, and had an abnormal sleep schedule. Since it would be a threat to validity to exclude patients with marked circadian disruption, she was enrolled. Because she collected samples at unusual times due to her typical schedule, as opposed to nonadherence to the study protocol, her samples were included in analyses.

Awakening samples with MEMS times more than 10 minutes after the self-reported awakening time were examined to explore the time lag between awakening and the provision of the awakening saliva sample. Actigraphy data were examined, and the awakening time estimated by actigraphy examination was compared with the saliva sample collection time. If both the self-reported awakening time and the awakening time estimated from actigraphy were more than 10 minutes from the sample provision time, a cortisol value for the awakening time estimated from actigraphy was computed. This value was estimated by regressing the wake and +30min cortisol values on collection time. When an awakening cortisol value was estimated statistically, the +30min sample was retained only if it was within a time window of 15-60 minutes post-awakening. If the wake cortisol value was estimated statistically and the +30min sample was deleted due to being outside the sample collection window, the wake cortisol value was used as the +30min sample, provided its collection time was within 15-60 minutes after the awakening time estimated from actigraphy. All cortisol analyses were first conducted using the original cortisol values, with no estimated values. All analyses were then repeated using the data set with estimated awakening cortisol values.

Cortisol values more than four standard deviations from the mean for that collection time were identified as outliers and examined for any possible confounders such as sample contamination, abnormally high nicotine or caffeine intake, or deviation from the requested sample time. Elimination of outliers was determined depending on confounding factors and degree of deviation from the mean.

Primary Analyses: Tests of Hypotheses

Hypothesis 1a: Cancer-related intrusions will be significantly and positively associated with circadian disruption, as measured by salivary cortisol and actigraphy.

A hierarchical regression equation predicting circadian disruption was calculated for each of the two measures of circadian disruption, salivary cortisol and rest/activity rhythms as measured by actigraphy. All analyses statistically controlled for two theoretically-derived variables, age at diagnosis and cancer stage. A third, empirically-derived control variable was included in regression models. This control variable was chosen from among demographic and medical variables that were found to be significantly and most strongly correlated with outcome measures in preliminary analyses. Control variables were entered on the first step of the regression equation. The mean of the daily intrusion scores was then entered on the second step. Outcome variables included the autocorrelation coefficient, dichotomy indices for time in bed and out of bed, mean log-transformed awakening cortisol, cortisol awakening response (CAR) slope, diurnal cortisol slope, and overall diurnal mean log-transformed cortisol.

Hypothesis 1b: Avoidant coping will moderate the relationship between cancer-related intrusive thoughts and circadian disruption.

If the R^2 value of IES in the equation calculated for hypothesis 1a was significant, a similar equation was calculated for hypothesis 1b. This equation utilized methods recommended by Baron and Kenny (Baron, 1986). Although a more recent conceptualization of moderators advised alternative analytical methods, these methods were not available for this analysis because they would require that intrusions precede

avoidant coping efforts temporally (Kraemer, Stice, & Kazdin et al., 2001). Because the study is cross-sectional, the temporal precedence requirement was not met.

The analytical procedure used to test hypothesis 1b includes mean-centered intrusion and avoidant coping scores (Baron & Kenny, 1986), as well as a cross-product of intrusion and avoidant coping composed of mean-centered scores. These terms are mean-centered to minimize collinearity with the interaction term. To limit the model to four predictor variables, only one additional control variable was selected by determining whether age at diagnosis or cancer stage was most strongly correlated with the outcome in a given regression equation. Due to concerns about overcontrolling noted in the analysis plan for hypothesis 1a, analyses were repeated using only the three predictors necessary to perform this test.

Hypothesis 2: Diurnal salivary cortisol slope and rest-activity rhythm obtained by actigraphy will be significantly and positively associated.

With conservative intent, a Spearman correlation was calculated to determine whether there is any association between variables yielded by two measures of circadian disruption, actigraphy and cortisol. Each actigraphy variable used as a measure of circadian disruption was correlated with each cortisol variable used as a measure of circadian disruption. Actigraphy variables included the 24-hour autocorrelation, the dichotomy indices both for time inside bed and time outside of bed. The cortisol variables included mean awakening cortisol, CAR slope, diurnal cortisol slope, and overall diurnal mean cortisol.

Because this analysis sought to characterize the relationship between two measures of the same construct, variables that likely influence circadian disruption and

were considered possible confounds in other analyses were not considered confounds for testing hypothesis 2. As a result, no tests attempted to determine whether the association of these two measures was independent of a third variable.

Secondary Analyses

To further the aim of conducting exploratory analyses of the relationships between intrusions, avoidant coping, and circadian disruption, secondary analyses were conducted. Because a maximum of 45 participants provided enough data to be included in some analyses, regression equations for all secondary analyses were limited to a total of four predictor variables, including age at diagnosis, cancer stage, an empirically selected third control variable, and the predictor of interest.

Modified Intrusions Analysis

As noted above, one factor analysis of the IES has reported that two items of the intrusions subscale load onto a separate sleep disturbance factor (Larsson, 2000). To investigate the possibility that these sleep disturbance items confound the predictor variable (intrusions) with the criterion variables (circadian disruption) in Hypothesis 1a and 1b of the primary analyses, an intrusions score without the two items that some researchers have conceptualized as sleep disturbance items (Larsson, 2000) was utilized as a predictor of circadian disruption.

Sleep Outcomes

The sleep intervals specified for each participant's actigraphy data were used to calculate several sleep variables, including sleep latency, total sleep interval, total sleep time, time awake after sleep onset, sleep efficiency, and awakenings. These outcomes were tested with intrusions as a predictor, and with age at diagnosis and cancer stage as control variables.

Avoidant Coping and Circadian Disruption

The avoidant coping score generated by the mean of the daily assessments was evaluated as a predictor of circadian disruption. Analytical methods were similar to those used with intrusions as a predictor of circadian disruption. All regression equations were limited to a total of three predictor variables.

Daily COPE Subscales Analysis

The Denial, Self-Distraction, and Behavioral Disengagement subscales that comprised the version of the Brief COPE completed on four consecutive mornings were tested separately as potential moderators of the effects of intrusions on circadian disruption. These analyses were only conducted when significant relationships between intrusions and circadian disruption were observed.

Secondary Cortisol Outcomes

All of the cortisol variables included in primary analyses were re-calculated with replacement of awakening cortisol values that were provided outside the ten minute time

window for these samples. If the awakening sample was not provided within a valid time period, the saliva collection time was regressed on the awakening and 30 minute post-awakening cortisol samples that had been provided. Using the slope from this linear regression, a cortisol value was estimated for the awakening time provided by actigraphy. The summary cortisol variables re-calculated with these estimated awakening values included in the dataset were analyzed in secondary analyses. The CAR % increase and CAR area under the awakening curve were also included in secondary cortisol analyses to supplement primary analysis of the CAR slope.

Cortisol and Sleep

Exploratory analyses explored the relationship between several diurnal cortisol values and the following night's sleep. Regression analyses used age at diagnosis and cancer stage as control variables. Cortisol variables used in previous analyses, as well mean bedtime cortisol values, were tested as predictors of the sleep variables used as outcomes in analyses described above. The bedtime cortisol values were added to explore whether high bedtime cortisol was related to disrupted sleep.

Removal of Patients Endorsing Depression

Because depression and symptoms associated with PTSD have been noted by some to have opposite effects on circadian cortisol rhythms (Miller, 2007), it is possible that the inclusion of participants experiencing depression suppressed the relationships between intrusions and circadian disruption tested in hypothesis 1a. To eliminate this possible confound, participants scoring more than 1.5 standard deviations from the mean

standardization sample score on the Profile of Mood States (POMS) depression subscale were deleted prior to repeated analyses of intrusions and circadian disruption. The standardization sample used was a sample of 400 participants stratified by age, gender and race according to United States census data (Nyenhuis et al., 1999). This standardization sample and method of classification was demonstrated to successfully classify people with HIV infection as having Major Depressive Disorder using the POMS depression scale (Patterson et al., 2006). The use of 1.5 standard deviations as a cut-score between clinical and nonclinical samples has been used with the Minnesota Multiphasic Personality Inventory-2 (MMPI-2; Butcher, Dahlstrom, Graham, Tellegen, & Kaemmer, 1989).

RESULTS

Sample Characteristics

Demographic and medical characteristics.

Study participants ranged in age from 21 to 79 years with an average of 53.4 years (SD = 13.2). Additional sociodemographic characteristics of the sample, including ethnicity, marital status, education, annual household income and employment status are presented in Table 2.

Table 2. Demographic characteristics of the sample (N=45)

Variable	Frequency	Percentage
Ethnicity		
White/Caucasian	25	56
African American	17	38
Native American	2	4
Asian	1	2
Marital Status		
Married	18	40
Divorced	12	27
Never Married	6	13
Widowed	8	18
Years of Education		
Middle School (8 years)	1	2
High School (12 years)	29	64
AA/Technical School (14 years)	5	11
College Degree (16 years)	4	9
Master's Degree (18 years)	4	9
Doctoral Training (20 years)	1	2

Variable	Frequency	Percentage
Income		
Less than $20,000	15	33
20,000 to 39,999	11	24
40,000 to 59,999	4	9
60,000 to 79,999	4	9
80,000 to 99,999	2	5
100,000 and Greater	5	11
Currently Employed		
Yes	23	51
No	22	49

Medical Data

All participants provided consent for medical record review. The frequencies and descriptive statistics for medical data obtained through chart review are presented in Table 3. Cancer stage provides information about disease characteristics and prognosis. Breast cancer stage is determined using the size of the tumor, the extent of regional lymph node involvement, and whether the disease has spread to other organs or tissue. Pathologic staging from chart review was used when available. Two patients did not have pathologic staging data available because surgery was not ultimately performed, and clinical staging based on the physical exam and imaging tests was used to determine staging for these two patients. Grade is a measure of the aggressiveness of the tumor as assigned by a pathologist. Only two patients elected to undergo lumpectomy, suggesting mastectomy was clearly the preferred option within the sample of women enrolled in this study. Due to the low frequency of lumpectomy chosen in this sample, group level analyses of surgical decision could not be completed.

Table 3. Staging and clinical data (N= 45)

Variable	Range	*Frequency*	*Percentage*
Stage	DCIS	3	6.7
	Stage I	20	44.4
	Stage IIA	4	8.9
	Stage IIB	3	6.7
	Stage IIIA	8	17.8
	Stage IIIB	1	2.2
	Stage IIIC	3	6.7
	Stage IV	3	6.7
Grade	1	3	6.7
	2	22	48.9
	3	17	37.8
	Missing	3	6.7
Tumor Size (T)	0	2	4.4
	TI	20	44.4
	T2	10	22.2
	T3	8	17.8
	T4	2	4.4
	Missing	3	6.7
Nodal Involvement (N)	0	26	57.8
	NI	7	15.6
	N2	7	15.6
	N3	3	6.7
	Missing	2	4.4
Metastatic Status (M)	M0	19	42.2
	M1	3	6.7
	Undetermined	23	51.1
Age at diagnosis (years)	53.4 (13.2) *(Mean/SD)*		21-79 *(range)*
Time since diagnosis (days)	18.8 (21.9) *(Mean/SD)*		0-122 *(range)*
Breast Cancer Type	Primary	43	95.6
	Recurrent	2	4.4

Variable	Range	*Frequency*	*Percentage*
Previous Breast Surgery	Yes	1	2.2
	No	44	97.8
History of Radiation*	Recent (past 2 mo.)	0	0
	Yes	2	4.4
	No	43	95.6
History of Chemotherapy	Recent (past 2 mo.)	0	0
	Yes	2	4.4
	No	43	95.6
History of Cancer at Other Body Site	Yes	1	2.2
	No	44	97.8
Comorbid Medical Condition**	Yes	20	44.4
	No	25	55.6
Menopausal Status	Pre-Menopausal	18	40.0
	Peri-Menopausal	3	6.7
	Post-Menopausal	24	53.3
Menstrual Phase	Pre-Menopausal, Follicular Phase	7	15.6
	Pre-Menopausal, Luteal Phase	9	20.0
	Pre-Menopausal, Phase Undetermined	2	4.4
	Peri-/Post-Meno. Estrogen Therapy	1	2.2
	Peri-/Post-Meno. No Estrogen	26	57.8
Oral Contraceptives	Yes	0	0
	No	45	100
Estrogen Replacement	Yes	1	2.2
	No	44	97.8
Surgical Decision	Mastectomy	39	86.7
	Lumpectomy	2	4.4
	Missing	4	8.9

Variable	N	*Mean (SD)*	*Range*
Systolic blood pressure	41	140.1 (20.4)	100-194
Diastolic blood pressure	40	83.9 (11.2)	63-115
Heart rate	41	83.0 (13.2)	64-120

* Two participants reported receiving radiation in the past. None of the participants reported receiving radiation in the past year.
** The participant endorsing a history of cancer at another site reported cervical cancer in 1985. Comborbid medical diagnoses included hypertension (11 participants), diabetes (9), history of myocardial infarction (2), arthritis (2), hypothyroidism (2), chronic obstructive pulmonary disease, scoliosis, chronic fatigue syndrome, seizures, skin lesions, chronic hives, scleroderma, local positive antinuclear antibody, supraventricular tachycardia, sarcoidosis, osteoarthritis, and asthma.

To ensure accurate recording of medications, participants were queried as to the medications they were taking. Frequencies for each class of medication taken by at least one participant in this study or those that are important to note because of conceptual links with major study variables, are presented in Table 4. The participant who reported taking Fluticasone, a systemic steroid, was deleted from all analyses including cortisol due to the influence of systemic steroids on cortisol assessments.

Table 4. Medications (N= 45)

Medication	*Frequency*	*Percentage*
Non-Steroidal Anti-inflammatory Agents	16	35.6
Antihypertensive Agents	13	28.9
Diuretics	11	24.4
Anti-Lipidemic	10	22.2
Antidepressants	8	17.8
Antidiabetic Agents	8	17.8
Cardiac Drugs	7	15.6
Opiate Agonists	6	13.3
Sleep Medications	5	11.1
Antihistaminic Agents	4	8.9
Anxiolytics	4	8.9
Bronchodilating Agents	4	8.9
Gastrointestinal Drugs	4	8.9
Thyroid Agents	3	6.7

Medication	*Frequency*	*Percentage*
Adrenergics	2	4.4
Analgesics	2	4.4
Antibiotics	2	4.4
Anticonvulsants	2	4.4
Antitussives	2	4.4
Benzodiazepine	2	4.4
Estrogen	2	4.4
Potassium Replacement	2	4.4
Sedatives/Tranquilizers	2	4.4
Urinary Anti-Spasmodic Agents	2	4.4
Vasodilating Agents	2	4.4
Anticoagulants	1	2.2
Antidiherreal Agents	1	2.2
Anti-psychotics	1	2.2
Antirheumatoids	1	2.2
Anti-Spasmodics	1	2.2
Anti-Viral Agents	1	2.2
Cathartics/Laxatives	1	2.2
Estrogen Replacement Therapy	1	2.2
Iron Replacements	1	2.2
Insulins	1	2.2
Leucotrine Antagonists Asthma Treatment	1	2.2
Prophylaxis (Preventive Medication)	1	2.2
Proton Pump Inhibitors	1	2.2
Para-Thyroid Hormones	1	2.2
Respiratory Muscle Relaxes	1	2.2
Skeletal Muscle Relaxants	1	2.2
Sulfonylureas	1	2.2
Systemic Contraceptives (Oral, patch, vaginal ring)	1	2.2
Systemic Steroids	1	2.2
Unclassified Therapeutic	1	2.2
Adrenals	0	0
Corticosteroids	0	0
Non-Systemic Contraceptives	0	0

Daily Assessments

Over a period of four days, participants provided self-reports of intrusions and avoidant coping, wore actigraphy devices, and provided saliva samples for cortisol assay.

Descriptive statistics for these daily assessments are presented in Table 5. The mean for daily IES assessments was 9.5 (SD = 5.6). The intrusions score was lower than those reported (14.5) by women recently informed that they required a breast biopsy (Lebel et al., 2003) and those reported by women who were within 1 year of breast cancer diagnosis but had completed surgery (Koopman et al., 2002), but similar to the intrusions score (9.61) reported in breast cancer patients an average of 19 months after bone marrow transplant (Jacobsen et al., 1998). The mean intrusions score reported in this study was lower than expected given the probable salience of the diagnosis such a short time after it had been communicated. Previous research identified the period immediately following diagnosis as a time of particularly high distress, but several possible explanations exist. First, daily assessments may yield different results than self-report measures prompting participants to report retrospectively over a longer period of time. Second, patients were often assessed in the first few days after diagnosis in this study, and many of the previous studies assessed women over a larger time window. Breast cancer-related intrusions may increase in the weeks following diagnosis as women engage in elaborative processing. Focus on breast cancer after diagnosis may promote association of the diagnosis with more environmental cues, prompting subsequent intrusions as those environmental cues are encountered in daily life. Intrusion levels may also be attributable to characteristics of the recruitment setting. Patients in this clinic often met with their physician for 60-90 minutes and received information related to their diagnosis and treatment. The communication of this information may have eased the process of deciding which surgical treatment to pursue and reduced concerns about outcomes that were unlikely given the characteristics of their illness.

The mean for avoidant coping assessments was 11.2 (SD = 4.1), which is comparable to levels observed using the same items with women seeking shelter after surviving domestic abuse (12.92) (Street, Gibson, & Holohan, 2005). Diagnosis of a life threatening illness and domestic abuse are both potentially traumatic events, so comparable levels of avoidant coping are not unexpected. However, potential differences between these events include the time of exposure to the stressor and the amenability of the stressor to active coping efforts. While most of the women in the current study had recently encountered the stressor for the first time, women suffering from domestic abuse may have endured this stressor for a long time before seeking shelter and could have even felt that the stressor was at or near its resolution because they had left the home. It is difficult to discern which stressor may have been perceived as more amenable to active coping. Although direct treatment of the tumor is largely undertaken by the patient's medical team, patients could engage in active coping such as seeking information related to their disease, reorganizing activities to pursue treatment and choosing treatments, and seeking emotional support from friends and family. Similarly, women suffering from domestic abuse over a long period of time may have abandoned most active coping efforts as they have proven ineffective in the past. Conversely, the act of seeking shelter is an example of active coping, and sampling these women may underrepresent avoidant coping levels in women experiencing domestic abuse.

Table 5. Descriptive data for daily measures

Variable	N	*Mean (SD)*	*Range*
Intrusions			
Intrusions	45	9.5 (5.6)	0-21
Coping			
Avoidant Coping	45	11.2 (4.1)	6-20.3
Self-distraction subscale	45	5.2 (1.9)	2-8
Denial subscale	45	3.2 (1.8)	2-7.75
Behavioral Disengagement Subscale	45	2.8 (1.4)	2-7.5
Sleep			
Nightly time in bed (hours)	42	7.26 (1.13)	4.35-10.02
Nightly time spent asleep (hours)	42	6.47 (1.32)	2.75-8.34
Nightly time spent awake after sleep onset (minutes)	42	48.8 (36.1)	15.67-168.75
Overall sleep efficiency (% of sleep interval spent awake)	42	88.6% (9.9)	50%-97%
Number of nightly awakenings	42	12.6 (6.0)	1.25-30
Sleep latency (minutes)	40	41.0 (30.1)	0-128.7
Circadian Disruption - Actigraphy			
24 hour autocorrelation coefficient	42	.280 (.176)	-.066-.721
Dichotomy index % for time in bed (D/I)	42	97.1% (3.6)	84.5%-100%
Dichotomy index % for time outside bed (D/O)	42	5.7% (5.2)	0.5%-20.05%
Circadian Disruption - Cortisol			
CAR % increase (µg/dL)	40	35.8% (63.0)	-74.1%-169.1%
CAR % increase$_E$ (µg/dL)	40	41.1% (75.2)	-74.1%-293.5%
Morning slope$_L$ (µg/dL)	42	.012 (.181)	-.611-.586
Morning slope$_{EL}$ (µg/dL)	42	.052 (.330)	-.611-1.728
Waking cortisol (µg/dL)	43	.354 (.278)	.087-1.628
Waking cortisol$_E$ (µg/dL)	43	.360 (.278)	.087-1.605
Area under the awakening curve$_L$ (µg/dL)	40	-1.762 (.661)	-3.693-(-0.184)
Area under the awakening curve$_{EL}$ (µg/dL)	40	-1.757 (.635)	-3.690-(-0.180)

Variable	N	*Mean (SD)*	*Range*
Diurnal cortisol $slope_L$ (µg/dL)	43	-.089 (.068)	-.246-.076
Diurnal cortisol $slope_{EL}$ (µg/dL)	43	-.092 (.072)	-.246-.076
Overall diurnal mean cortisol (µg/dL)	43	.241 (.146)	.088-.911
Overall diurnal mean $cortisol_{EL}$ (µg/dL)	43	.242 (.145)	.088-.904
Bedtime cortisol $(µg/dL)_L$	42	.121 (.121)	.015-.535

"E" subscripts are used to denote summary cortisol variables calculated with the estimated awakening cortisol value included. "L" subscripts are used to denoted cortisol values that are presented after log transformation to correct for non-normal distribution.

Preliminary Analyses

Normality

Potential control variables, predictors, and outcome variables were evaluated by examining a histogram and boxplot for each variable to determine whether they met the normality assumption for Pearson correlations. For all variables that did not meet this assumption, Spearman correlations were used to evaluate bivariate relationships.

Control variables

Both theoretical and empirical methods were used to identify potential control variables. Age at diagnosis and cancer stage were adjusted in all analyses due to likely associations with both the predictor and outcome variables. Bivariate correlations of racial background, education, income, weight, systolic blood pressure, diastolic blood pressure, tumor size, nodal involvement, estrogen receptor status at the time of diagnosis, progesterone receptor status at diagnosis, human epidermal growth factor receptor

(her2/neu) status at diagnosis, grade at diagnosis, time since diagnosis, each class of medications taken by at least 5% of the sample, and all medications taken for the purpose of sleep. Of the variables that exhibited significant correlations with the outcome variable, the control variables with the highest correlations were used as covariates in the calculation of regression equations and partial correlations. Bivariate correlations between demographic variables and outcome variables can be found in Table 6. Potential control variables and outcome variables were evaluated to determine whether they were normally distributed. Non-normally distributed variables were examined using Spearman's r, as noted on Table 6. Preliminary analyses of medical data as potential control variables are presented in Table 7. All patients included in any analysis are presented in these tables, resulting in 45 total participants.

Table 6. Bivariate correlations of outcome variables with demographic and biological characteristics (N=45)

	Age at diagnosis	Race	Education	Income	Weight	Systolic BP	Diastolic BP	Performance Status
Rest/activity autocorrelation	.126	-.337[1]*	.316*	.490[1]**	-.297	-.055[1]	-.133[1]	.356[1]*
Dichotomy index –								
% for time inside bed	-.229[1]	-.062[1]	.195[1]	.342[1]*	-.270[1]	-.311[1]	-.086[1]	.116[1]
% for time outside bed	.029[1]	.143[1]	-.289[1]	-.267[1]	.048[1]	.101[1]	-.058[1]	-.252[1]
Nightly time asleep	-.243	-.175[1]	.131	.280[1]	-.366*	-.119[1]	.003[1]	-.084[1]
Awakenings	-.395*	.167[1]	.003	.149[1]	.013	.068[1]	.267[1]	-.134[1]
Wake after sleep onset	-.042	.123[1]	-.059[1]	-.045[1]	.091[1]	.215[1]	.100[1]	-.009[1]
Sleep efficiency	-.078[1]	-.099[1]	.116[1]	.054[1]	-.103[1]	-.150[1]	.020[1]	-.019[1]
Sleep onset latency	.053[1]	.074[1]	-.378[1]*	-.051[1]	.055[1]	-.015[1]	-.119[1]	-.223[1]
Mean waking cortisol$_L$	.262[1]	.023[1]	.082[1]	.119[1]	-.007[1]	.069[1]	-.063[1]	.059[1]
Mean waking cortisol$_{EL}$	.307[1]*	-.083[1]	.002[1]	.081[1]	.142[1]	.006[1]	-.143[1]	.067[1]
Morning slope$_L$	.044[1]	.361[1]*	-.137[1]	-.206[1]	-.140[1]	.162[1]	.120[1]	-.103[1]
Morning slope$_{EL}$	-.064[1]	.270[1]	-.176[1]	-.045[1]	-.165[1]	.071[1]	.090[1]	-.076[1]
CAR % increase	-.191[1]	.144[1]	.039[1]	.079[1]	-.205[1]	-.002[1]	.302[1]	-.015[1]
CAR % increase$_E$	-.238[1]	.174[1]	.028[1]	.120[1]	-.230[1]	.004[1]	.337[1]*	-.036[1]
Area under waking curve$_L$	.167[1]	.030[1]	.024[1]	.030[1]	-.180[1]	..045[1]	-.010[1]	.034[1]
Area under waking curve$_{EL}$	.161[1]	.039[1]	.026[1]	.033[1]	-.196[1]	.051[1]	.051[1]	.083[1]
Diurnal cortisol slope$_L$	-.032[1]	.199[1]	-.197[1]	-.184[1]	.049[1]	.028[1]	.073[1]	-.271[1]
Diurnal cortisol slope$_{EL}$	-.053[1]	.214[1]	-.152[1]	-.110[1]	-.011[1]	.055[1]	.092[1]	-.227[1]
Mean overall diurnal cortisol$_L$	.216[1]	.056[1]	-.058[1]	.069[1]	-.145[1]	-.004[1]	..103[1]	-.059[1]
Mean overall diurnal cortisol$_{EL}$	.249[1]	.011[1]	-.119[1]	.032[1]	-.054[1]	-.002[1]	-.095[1]	-.098[1]

	Age at diagnosis	Race	Education	Income	Weight	Systolic BP	Diastolic BP	Performance Status
Bedtime Cortisol$_L$	.055$_1$	.235$_1$	-.152$_1$	-.129$_1$	.086$_1$	.066$_1$	.048$_1$	-.284$_1$

"E" subscripts are used to denote summary cortisol variables calculated with the estimated awakening cortisol value included.
"L" subscripts are used to denote cortisol values that are presented after log transformation to correct for non-normal distribution.
* $p < .05$.
** $p < .01$
"1" subscripts are used to denote Spearman correlations
Race is a dichotomous variable dividing the sample into Caucasian (scored as a 0) and minority groups (scored as a 1). A higher score indicates that the variable is correlated with a minority racial background.

Table 7..Bivariate Correlations for Medical Variables (N = 45)

	Summary Stage	Tumor Size at diagnosis	Nodal Involvement	ER+ at diagnosis	PR+ at diagnosis	Her2+ at diagnosis	Tumor Grade	Time Since Diagnosis
Rest/activity autocorrelation	-.028	$.168_1$	$.188_1$	-.007	.040	-.311	-.123	.139
Dichotomy index –								
% for time inside bed	$.058_1$	$.273_1$	$.057_1$	$-.022_1$	$-.049_1$	$.060_1$	$-.093_1$	$.116_1$
% for time outside bed	$-.126_1$	$-.273_1$	$-.043_1$	$.049_1$	$.066_1$	$.094_1$	$.142_1$	$-.133_1$
Nightly time asleep	.239	$.449_1$**	$.247_1$	-.086	-.113	-.180	.018	$.315_1$*
Awakenings	.013	$.096_1$	$.109_1$	.021	.016	.041	.184	-.068
Wake after sleep onset	$.119_1$	$-.052_1$	$.116_1$	$-.055_1$	$-.033_1$	$.094_1$	$.227_1$	-.257
Sleep efficiency	$-.035_1$	$.153_1$	$-.046_1$	$.082_1$	$.060_1$	$-.051_1$	-.146	.345*
Sleep onset latency	$-.113_1$	$-.135_1$	$-.048_1$	$-.178_1$	-.050	.179	.088	-.211
Mean waking $cortisol_L$	$.048_1$	$.035_1$	.105	$-.170_1$	$-.224_1$	$.101_1$	$.185_1$	$.028_1$
Mean waking $cortisol_{EL}$	$.009_1$	$-.016_1$	$.081_1$	$-.131_1$	$-.125_1$	$.000_1$	$.153_1$	$.070_1$
Morning $slope_L$	$.002_1$	$-.068_1$	$.146_1$	$-.231_1$	$-.270_1$	$.153_1$	$.232_1$	$-.176_1$
Morning $slope_{EL}$	$.050_1$	$-.021_1$	$.203_1$	$-.202_1$	$-.250_1$	$.068_1$	$.287_1$	$-.136_1$
CAR % increase	$.092_1$	$.070_1$	$.007_1$	$.267_1$	$-.082_1$	$.202_1$	$.080_1$	$-.105_1$
CAR % $increase_E$	$.131_1$	$.111_1$	$.053_1$	$.259_1$	$-.082_1$	$.313_1$	$.136_1$	$-.126_1$
Area under waking $curve_L$	$.093_1$	$.034_1$	$-.018_1$	$.007_1$	$-.282_1$	$.192_1$	$.026_1$	$.013_1$
Area under waking $curve_{EL}$	$.120_1$	$.072_1$	$.011_1$	$-.037_1$	$-.254_1$	$.243_1$	$.088_1$	$.001_1$
Diurnal cortisol $slope_L$	$-.069_1$	$-.114_1$	$-.212_1$	$.234_1$	$-.065_1$	$.391_1$*	$-.306_1$	$-.034_1$
Diurnal cortisol $slope_{EL}$	$-.030_1$	$-.072_1$	$-.176_1$	$.221_1$	$-.071_1$	$.391_1$*	$-.295_1$	$-.039_1$
Mean diurnal $cortisol_L$	$-.055_1$	$-.101_1$	$-.110_1$	$.032_1$	$-.226_1$	$.342_1$*	$-.035_1$	$-.089_1$
Mean diurnal $cortisol_{EL}$	$-.086_1$	$-.152_1$	$-.139_1$	$.051_1$	$-.202_1$	$.293_1$	$-.046_1$	$-.080_1$

"E" subscripts are used to denote summary cortisol variables calculated with the estimated awakening cortisol value included.
"L" subscripts are used to denoted cortisol values that are presented after log transformation to correct for non-normal distribution.
"1" subscripts denote Spearman correlation
* $p < .05$
** $p < .01$

Table 7 notes that larger tumor size was significantly correlated with more nightly sleep (Spearman's $r = .449$, $p < .01$). Not only is it surprising that these variables are significantly correlated, but the correlation is in an unexpected direction. There is no obvious conceptual reason why a larger tumor should be related to increased time spent asleep. As a result, the distribution of nightly sleep was examined in a boxplot illustrated in figure 5 below. Nightly sleep is slightly negatively skewed, as two participants lie below the error bar. Examination of tumor size categories for these patients revealed that one was classified as T = 1, the modal classification for tumor sizes in this study, and the other was classified as T = 3, a value that would suggest a negative correlation between tumor size and sleep. As a result these two patients did not account for the correlation of tumor size and sleep. This distribution also indicates that there were no participants who were outliers with abnormally high levels of sleep and large tumor sizes. It is possible that this correlation is a spurious one due to the relatively small sample size. In any case, no association of tumor size with overall 24-hour rhythms was observed, so any effect of tumor size would be limited to sleep outcomes. Nevertheless, future studies might note the relationship between these variables and build on the available understanding of their relevance to tumors and sleep.

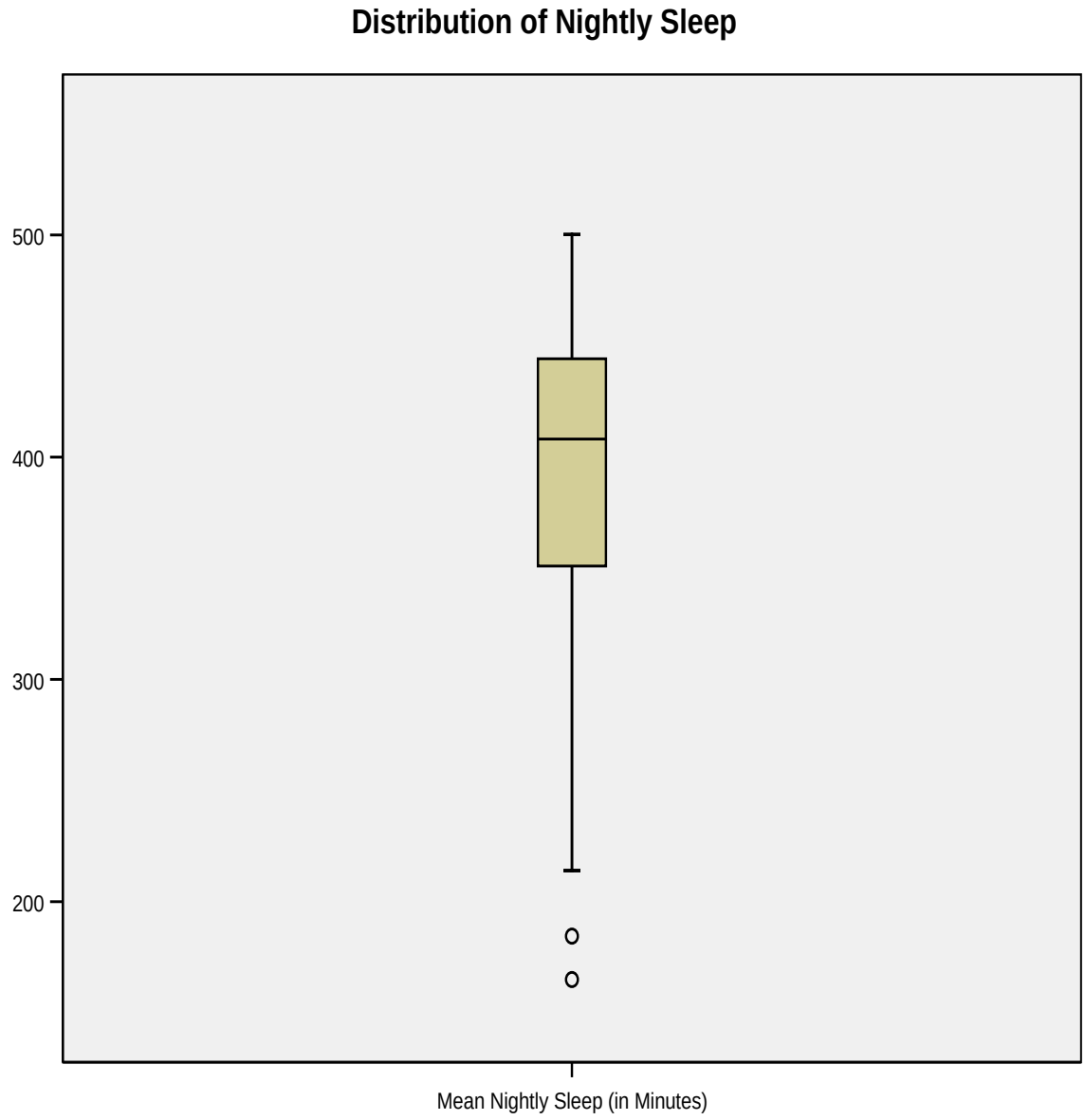


Figure 5. Distribution of mean nightly sleep in minutes for the sample. The line in the middle of the box represents the median, and the edges of the box represent quartiles. The error bars represent a 95% confidence interval.

Evaluation of Missing Cortisol Data

One participant was excluded from all analyses involving cortisol due to nonadherence to the protocol. Of the 45 patients included in at least a portion of the

primary analyses involving cortisol variables, 86.7% of all possible cortisol samples were completed, judged to be provided at a valid time, without contamination, and with a valid value. The number of missing cortisol samples was evaluated in terms of its relationship with disease stage and intrusions to explore whether samples were missing for systematic, as opposed to random, reasons. The number of missing cortisol samples was not significantly correlated with disease stage (Spearman's $r = .043$, $p = .781$) or intrusions (Spearman's $r = .049$, $p = .751$).

Next, the number of missing cortisol samples was correlated with cortisol outcome variables to determine whether missing data might alter the summary variables used in subsequent analyses. The number of missing samples was significantly correlated with the diurnal cortisol slope (Spearman's $r = .375$, $p = .012$). More missing values were correlated with a flatter diurnal cortisol slope. This relationship remained significant using the diurnal cortisol slope calculated with estimated awakening cortisol times included (Spearman's $r = .359$, $p = .017$). More missing samples were also significantly correlated with elevated average bedtime cortisol values (Spearman's $r = .508$, $p = .001$). Analyses finding a significant relationship with one of these variables as an outcome were followed up with analyses that controlled for the number of missing samples to investigate whether the number of missing samples was a confound.

Although the MEMS collection times and self-reported collection times were highly correlated (Spearman's $r = .977$, $p < .01$), analyses sought to determine whether differences between these two collection time measures came about systematically. Correlations with disease stage (Spearman's $r = -.007$, $p = .965$) and intrusions (Spearman's $r = .236$, $p = .143$), as measured by the daily IES measure, revealed no

statistically significant relationship, suggesting that the differences between the two measures of collection time would not confound results.

Primary Analysis for Testing Main Hypotheses

Hypothesis 1a: Cancer-related intrusions will be significantly and positively associated with circadian disruption, as measured by salivary cortisol and actigraphy.

Hierarchical regression models were utilized to examine the hypothesis that intrusions were significantly associated with circadian disruption. All analyses statistically controlled for two theoretically-derived variables, age at diagnosis and cancer stage. A third, empirically-derived control variable was included in regression models. This control variable was chosen from among demographic and medical variables that were found to be significantly and most strongly correlated with outcome measures in preliminary analyses. The mean of the daily intrusion scores was then entered on the second step.

Outcome variables for primary analyses included the autocorrelation coefficient, dichotomy indices for time in bed and out of bed, mean awakening cortisol, cortisol awakening response (CAR) slope, CAR slope, diurnal cortisol slope, overall diurnal mean cortisol, and bedtime cortisol level. A total of nine outcome variables were evaluated, including three actigraphy variables and six cortisol variables.

In the hierarchical regression model of intrusions predicting circadian disruption, using autocorrelation as the outcome measure, control variables entered in the first step (age, stage, and income) explained a significant amount of variance as a group (ΔR^2 = .222; $F(3,35) = 3.335$, $p = .030$). The addition of intrusions ($\Delta R^2 = .146$; $F(1,34) = 7.853$,

p = .008) accounted for a significant proportion of the remaining variance, with intrusions being related to a lower autocorrelation (partial r = -.433), a marker of less pronounced circadian rhythm. The entire 4-variable model was related to the autocorrelation as well ($F(4,34) = 4.954$, $p = 0.003$). These statistics, as well as statistics for other circadian rhythm variables derived from actigraphy, are presented in Table 8. A scatterplot of the bivariate relationship between the 7-item version of the intrusions subscale of the IES and the autocorrelation is depicted in Figure 6. Regression equations with other circadian disruption variables as outcomes revealed no other associations of intrusions with circadian disruption that were independent of control variables, including both actigraphy and cortisol outcomes.

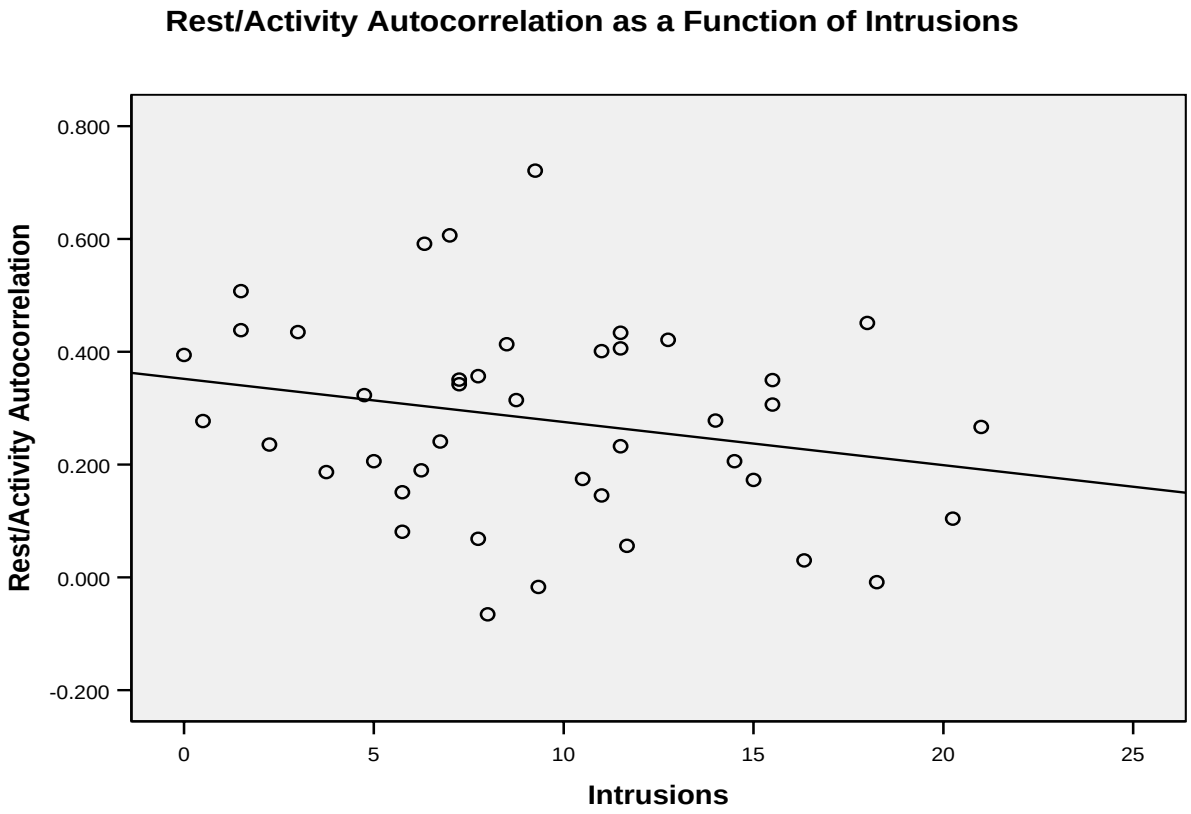
In the hierarchical regression model of intrusions predicting circadian disruption, using the mean CAR % increase as the outcome measure, control variables entered in the first step (age and stage) did not explain a significant amount of variance as a group ($\Delta R^2 = .043$; $F(2,37) = 0.839$, $p = .440$). The addition of intrusions ($\Delta R^2 = .101$; $F(1,36) = 4.245$, $p = .047$) accounted for a significant proportion of the remaining variance, with intrusions being related to an elevated CAR % increase (partial r = .325), a marker of less pronounced circadian rhythm. The entire 4-variable model was related to the CAR % increase as well ($F(3,36) = 2.024$, $p = .128$). The addition of intrusions on the second step of a model predicting CAR % increase with estimated awakening values included also contributed significantly to the explanatory power of the model ($\Delta R^2 = .134$; $F(1,36) = 5.928$, $p = .020$), with intrusions again being associated with elevated CAR % increase (partial r = .376).

Table 8. Summary of hierarchical regression analyses entering the 7-item intrusions measure as a predictor of circadian disruption measured by actigraphy.

Variable	B	SE B	ß	R^2	ΔR^2	p of ΔR^2	N
Autocorrelation							
Step 1				.222	.222	.030	39
Age	.002	.002	.147				
Stage	.007	.011	.093				
Income	.044	.014	.470*				
Step 2				.368	.146	.008	
Intrusions	-.013	.004	-.414*				
Dichotomy Index Inside (D/I)							
Step 1				.099	.099	.262	42
Age	.013	.049	.048				
Stage	.104	.271	.061				
Anti-lipidemic agents	-3.255	1.569	-.372*				
Step 2				.024	.122	.322	
Intrusions	-.110	.110	-.162				
Dichotomy Index Outside (D/O)							
Step 1				.233	.233	.017	42
Age	-.063	.063	-.158				
Stage	-.054	.363	-.022				
Opiate Agonists	7.849	2.408	.491**				
Step 2				.246	.013	.422	
Intrusions	.064	.136	.073				

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

Figure 6. Illustration of the bivariate relationship between intrusions and the rest/activity autocorrelation (N = 42).



The regression line for the bivariate relationship illustrated in Figure 6 had the following equation: y = -0.008x + .352. Partial r = -.233, p = .137.

Modified Intrusions Measure

The two items on the IES that some have argued assess sleep disturbance, as opposed to intrusions, were removed from the IES, and a new intrusions score for the

four collection days was calculated using a summary score of the remaining five items. This intrusions score was used to explore whether the two "sleep" items had accounted for the relationship between intrusions and circadian rhythms. Using this modified scale, results were similar to those observed with the full, 7-item scale. The addition of intrusions on the second step of a hierarchical regression predicting the autocorrelation significantly added to predictive power of the model ($\Delta R^2 = .113$; $F(1,34) = 5.798$, $p = .022$), such that intrusions were related to a lower autocorrelation (partial $r = -.382$). The overall, four variable model was also predictive of the autocorrelation ($F(4,38) = 4.293$, $p = .006$).

In contrast to the results observed using the 7-item version of the intrusions subscale, addition of the 5-item intrusions subscale on the second step was not predictive of the CAR % increase ($\Delta R^2 = .088$; $F(1,36) = 3.634$, $p = .065$), though it was a significant, independent predictor of CAR % increase when estimated awakening values were included ($\Delta R^2 = .112$; $F(1,36) = 4.816$, $p = .035$). Other regression equations examining intrusions as a predictor of circadian disruption did not reveal significant, independent effects of the 5-item intrusions subscale on circadian disruption.

Hypothesis 1b: Avoidant coping will moderate the relationship between cancer-related intrusive thoughts and circadian disruption.

To evaluate daily avoidant coping reports as potential moderators of the relationship between intrusions and circadian disruption, only the significant relationships observed in analyses from hypothesis 1a were tested. Because a significant association of intrusions with the autocorrelation was observed, a test of moderation was performed.

Age at diagnosis was used as a covariate and entered on the first step with the mean-centered avoidant coping variable and the mean-centered intrusions variable. The intrusions and avoidant coping variables were moderately correlated (Pearson's r = .554, p < .001). In this hierarchical regression model, age was entered on the first step with the mean-centered intrusions and avoidant coping variables. These variables did not explain a significant amount of variance as a group (ΔR^2 = .188; F(3,38) = 2.704, p = .060). In addition, age (partial r = .009, p = .958) and mean-centered intrusions (partial r = .005, p = .975) covariates were not significant predictors individually. Mean-centered avoidant coping (partial r = -.358, p = .030) was a significant predictor individually. Using the mean-centered avoidant coping and intrusions scores, a cross-product of these variables was calculated and entered on the second step of this regression equation. This cross-product did not account for a significant proportion of the remaining variance (ΔR^2 = .005; F(1,34) = 2.030, p = .662). It should be noted that avoidant coping was no longer a significant individual predictor of the rest/activity autocorrelation (partial r = -.305, p = .070) after the interaction term was added to the model. In a separate model, the addition of a cross product between the mean-centered 5-item version of the intrusions subscale and the autocorrelation on the second step of a regression equation also did not contribute significantly to the predictive power of the model (ΔR^2 = .002; F(1,37) = 0.067, p = .796).

Because intrusions were related to the CAR % increase in hypothesis 1a analyses, a model testing avoidant coping as a moderator of this relationship was tested. In this model, age (partial r = -.157, p = .348), mean-centered intrusions (partial r = .192, p = .247), and mean-centered avoidant coping (partial r = .155, p = .352) did not explain a

significant amount of variance individually or as a group (ΔR^2 = .159; F(3,36) = 2.275, p = .096) and neither did the addition of the interaction between intrusions and avoidant coping (ΔR^2 = .064; F(1,35) = 2.887, p = .098). Similar results were observed when using the interaction between intrusions and avoidant coping to predict CAR % increase with estimated awakening values included (ΔR^2 = .036; F(1,35) = 1.597, p = .215).

Hypothesis 2: Diurnal salivary cortisol slope and rest-activity rhythm obtained by actigraphy will be significantly and positively associated.

Spearman correlations between actigraphy and cortisol measures of circadian disruption were calculated to explore this relationship. Actigraphy measures included the rest/activity autocorrelation and the dichotomy indices for time in and out of bed. Cortisol variables included the awakening cortisol value, CAR slope, diurnal cortisol slope, mean diurnal cortisol, and bedtime cortisol value. All correlations are shown in Table 9. Significant correlations involving the diurnal cortisol slope or bedtime cortisol level were followed up by partial correlations controlling for the number of missing cortisol values because the number of missing values was correlated with these two measures and presented a possible confound. The results of partial correlations are presented in Table 10.

A higher autocorrelation was correlated with a steeper decline in the diurnal cortisol slope (Spearman's r = -.613, p < .001), both indications of circadian rhythmicity. This effect was independent of the number of missing cortisol values (partial r = -.638, p < .001). A higher autocorrelation was also correlated with a lower bedtime cortisol value

(Spearman's r = -.459, p = .003), an effect that was independent of the number of missing cortisol samples (partial r = -.476, p = .002).

Table 9. Actigraphy and Cortisol Correlations (N = 41)

	24 hour Autocorrelation	**Dichotomy Index Inside**	**Dichotomy Index Outside**
Mean Waking $Cortisol_L$	.273	.039	-.183
Morning Cortisol $Slope_L$	-.238	-.276	.348*
Diurnal Cortisol $Slope_L$	-.613**	-.302	.498**
Mean Diurnal $Cortisol_L$	-.078	-.114	.165
Bedtime $Cortisol_L$	-.459**	-.273	.431**

"L" subscripts are used to denoted cortisol values that are presented after log transformation to correct for non-normal distribution.
* p < .05, ** p < .01
All correlations calculated using Spearman's r

Significant correlations were noted between a higher D/O and a flatter diurnal cortisol slope (Spearman's r = .498, p = .001), independent of missing cortisol samples (partial r = .471, p = .003). D/O was also associated with a steeper increase in the morning cortisol slope (Spearman's r = .348, p = .028), and elevated bedtime cortisol (Spearman's r = .431, p = .006), an effect that was also independent of missing cortisol values (partial r = .408, p = .011). Because D/O reflects the amount of activity when out of bed that falls below the median activity level for time in bed, a high D/O suggests circadian disruption. Other results are presented in Tables 9 and 10.

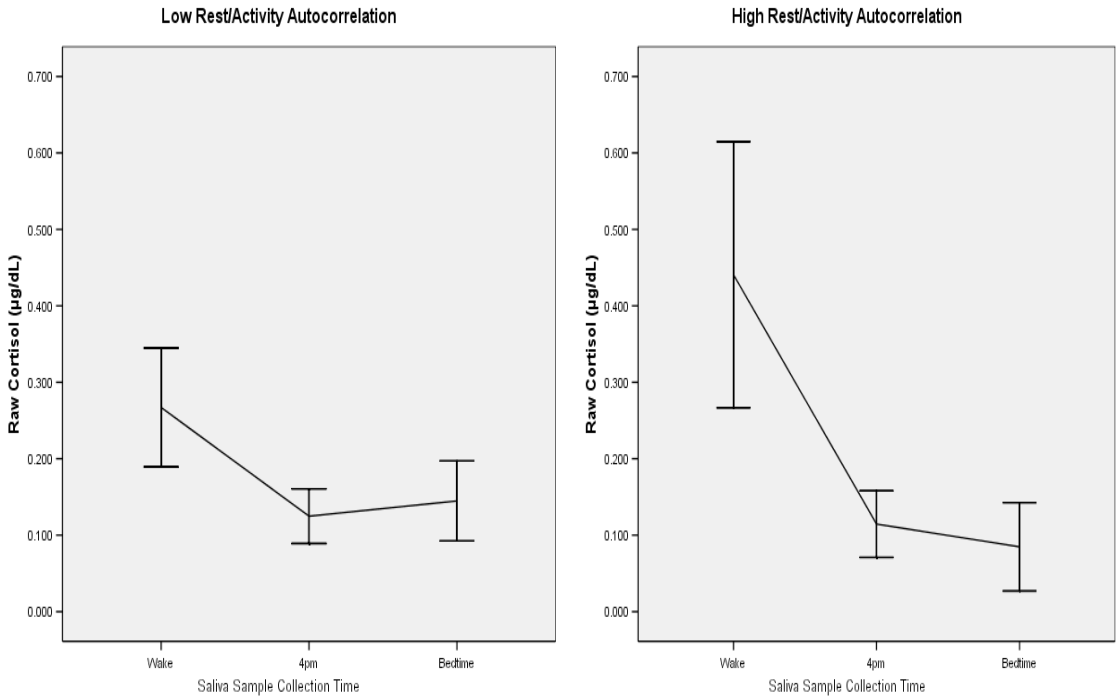
Table 10. Summary of partial correlations between actigraphy and cortisol. The number of missing cortisol samples was statistically controlled.

Actigraphy	Cortisol	CV	partial r	p
Autocorrelation	diurnal slope$_L$	missing samples	-.638	<.001
Autocorrelation	diurnal slope$_{EL}$	missing samples	-.591	<.001
Autocorrelation	bedtime cortisol$_L$	missing samples	-.476	.002
D/O	diurnal slope$_L$	missing samples	.471	.003
D/O	diurnal slope$_{EL}$	missing samples	.436	.006
D/O	bedtime cortisol$_L$	missing samples	.408	.011

"L" subscripts are used to denoted cortisol values that are presented after log transformation to correct for non-normal distribution. "E" subscripts are used to denote summary cortisol variables calculated with the estimated awakening cortisol value included.
* $p < .05$
** $p < .01$

Figure 7 illustrates the relationship between the rest/activity autocorrelation and raw cortisol values throughout the day. Solely for the purpose of illustration, the sample was split into "Low" and "High" autocorrelation groups using a median split. The two groups derived from the median split of the autocorrelation were not used in any data analyses.

Figure 7. Contrasts between raw diurnal cortisol values for participants characterized by a median split of rest/activity autocorrelations (N = 20 for each group).



Legend. A median split was used to divide the sample into low and high autocorrelation groups. These groups were created solely to aide in illustrating the relationship between the autocorrelation and cortisol values, and the autocorrelation median split was not used for any data analyses. All cortisol values are raw, untransformed values and are in µg/dL.

Secondary Analyses

Secondary Analysis #1: Sleep Variables from Actigraphy as Outcomes

Actigraphy data were used to calculate the mean time spent asleep each night, the mean amount of time awake after sleep onset, the mean sleep onset latency, the mean number of awakenings, and the percentage of time spent asleep each night. These variables were tested as outcomes in analyses similar to those used with circadian disruption variables in previous analyses. The intrusion score, with and without the two

"sleep" items was tested as a predictor of sleep outcomes. Analyses were performed with age and stage as control variables and a third, empirically selected control variable. The predictor of interest was entered on the second step. Intrusions were not significantly related to sleep in any of these analyses.

Secondary Analysis #2: Direct Effects of Avoidant Coping on Circadian Disruption

Avoidant Coping Summary Scale

To determine whether avoidant coping was related to circadian disruption directly, as opposed to moderating the effects of intrusions on circadian disruption, regression analyses similar to those employed to test hypothesis 1a were used with avoidant coping as the predictor entered on the second step. Regression equations were calculated with a third, empirically selected control variable. Separate regression equations were calculated for each of the following outcomes: rest/activity autocorrelation, D/I, D/O, sleep time, awakenings, wake after sleep onset, sleep efficiency, sleep onset latency, awakening cortisol value, CAR morning slope, CAR % increase, area under the awakening cortisol curve, diurnal cortisol slope, and mean diurnal cortisol, and bedtime cortisol value. All cortisol equations were calculated with and without awakening values estimated using linear modeling.

The autocorrelation was regressed on age, stage, and income on the first step of a hierarchical regression equation, and these control variables explained a significant amount of variance as a group ($\Delta R^2 = .222$; $F(3,35) = 3.335$, $p = .030$). Similarly, the addition of avoidant coping on the second step predicted the autocorrelaion ($\Delta R^2 = .098$;

$F(1,34) = 4.896$, $p = .034$), such that avoidant coping was associated with circadian disruption (partial $r = -.355$).

Table 11. Summary of Regression Equations Noting a Significant Relationship Between Avoidant Coping and Actigraphy Measures of Circadian Disruption.

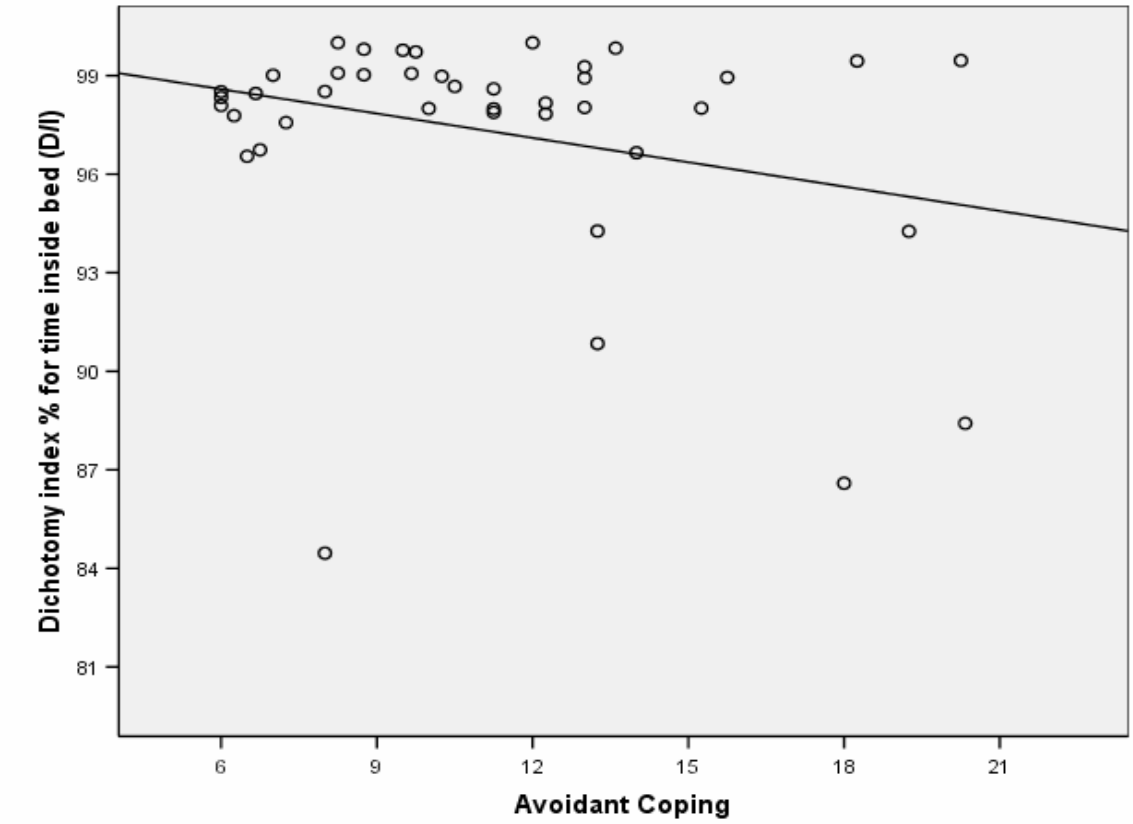
Variable	B	SE B	ß	R^2	ΔR^2	p of ΔR^2	N
Autocorrelation							
Step 1				.222	.222	.030	39
Age	.002	.002	.135				
Stage	.007	.011	.085				
Income	.036	.014	.384*				
Step 2				.320	.098	.034	
Avoidant Coping	-.013	.006	-.333*				
Dichotomy/Inside (D/I)							
Step 1				.099	.099	.262	42
Age	.007	.045	.025				
Stage	.123	.248	.072				
Anti-Lipidemic Agents	-3.534	1.411	-.404*				
Step 2				.267	.168	.006	
Avoidant Coping	-.366	.125	-.422*				

* $p < .05$

In a hierarchical regression controlling for age, stage, and anti-lipidemic medication, the control variables entered on the first step did not explain a significant amount of variance in D/I as a group ($\Delta R^2 = .099$; $F(3,38) = 1.385$, $p = .262$). However, when avoidant coping was entered on the second step, it was a significant predictor of D/I ($\Delta R^2 = .168$; $F(1,37) = 8.496$, partial $r = -.432$, $p = .006$), such that avoidant coping was related to less time in bed in which the activity level was below the median activity level when not in bed. The bivariate relationship between avoidant coping and D/I is represented in Figure 8. A lower D/I is likely characteristic of disrupted circadian

rhythmicity. The entire, four variable model was not related to D/I ($F(4,37) = 3.368$, $p = .019$). Results for actigraphy variables can be seen in Table 11. Avoidant coping was not independently related to any other circadian disruption outcomes.

Figure 8. Illustration of the bivariate relationship between avoidant coping and the dichotomy index for time in bed (D/I) (N = 41).



The regression equation for the bivariate relationship is $y = -.366x + 101.398$. Partial $r = -.432$, $p = .006$.

Secondary Analysis #3: Avoidant Coping Subscales and Circadian Disruption

Average scores on daily avoidant coping subscales were calculated and explored as predictors of circadian disruption. Avoidant coping subscales included self-distraction,

denial, and behavioral disengagement. Analytic procedures were identical to those used for the summary daily avoidant coping score used as a predictor in secondary analysis #2.

Self-Distraction

With log-transformed area under the awakening cortisol curve (MAUC) as the outcome, age and stage did not collectively predict MAUC (R^2 = .177; F(3,36) = 2.576, p = .069), but the addition of self-distraction on the second step did (ΔR^2 = .106; F(1,35) = 5.186, p = .029). Self-distraction was related to increased MAUC (partial r = .359). Similar results were observed when awakening values estimated using linear modeling were included in the calculation of the area under the awakening cortisol curve, as the addition of self-distraction was related to higher MAUC (ΔR^2 = .119; F(1,35) = 6.151, partial r = .387, p = .018). Significant results observed in models using self-distraction as a predictor of circadian disruption are presented in Table 12.

When the log-transformed average awakening cortisol value was tested as an outcome, the collection of age, stage, and bronchodilating medication was not related to awakening cortisol (R^2 = .107; F(2,40) = 2.385, p = .105), but the addition of self-distraction on the second step was significantly associated with a higher awakening cortisol level (ΔR^2 = .088; F(1,39) = 4.280, partial r = .314, p = .045). Similar results were observed when estimated awakening values were included, as the addition of self-distraction on the second step was associated with a higher awakening cortisol level (ΔR^2 = .091; F(1,39) = 4.377, partial r = .318, p = .043).

No other significant relationships were observed in models using self-distraction as a predictor of circadian disruption, including all analyses with actigraphy outcomes.

Table 12. Summary of Regression Equations Showing a Significant Relationship between Self-distraction and Cortisol Awakening Response.

Variable	B	SE B	ß	R^2	ΔR^2	p of ΔR^2	N
Area Under Awakening Curve (MAUC)							
Step 1				.177	.177	.069	40
Age	.009	.008	.187				
Stage	.049	.056	.144				
Benzodiazepines	.966	.471	.322*				
Step 2				.283	.106	.029	
Self-Distraction	.115	.051	.344*				
MAUC with Estimated Waking Values$_E$							
Step 1				.203	.203	.040	40
Age	.011	.008	.218				
Stage	.060	.052	.184				
Benzodiazepines	.933	.445	.324				
Step 2				.322	.119	.018	
Self-Distraction	.117	.047	.365*				
Mean Awakening Cortisol							
Step 1				.107	.107	.105	43
Age	.014	.007	.302				
Stage	.070	.049	.223				
Step 2				.195	.088	.045	
Self-Distraction	.097	.047	.311*				
Mean Awakening Cortisol$_E$							
Step 1				.101	.101	.119	43
Age	.015	.008	.307				
Stage	.065	.052	.193				
Step 2				.192	.091	.043	
Self-Distraction	.104	.050	.315*				

"E" subscripts are used to denote summary cortisol variables calculated with the estimated awakening cortisol value included.

* $p < .05$

Denial

In a hierarchical regression exploring denial as a predictor of D/I, control variables including age, stage, and anti-lipidemic medication entered on the first step did not significantly predict D/I (ΔR^2 = .099; F(3,38) = 1.385, p = .262). Denial entered on the second step independently predicted D/I (ΔR^2 = .222; F(1,37) = 12.119, p = .001), such that denial was associated with a lower D/I (partial r = -.497). The entire, four variable model was also related to D/I (F(4,37) = 4.373, p = .005). Regression equations yielding a significant effect of denial on circadian disruption are summarized in Table 13.

Table 13. Summary of Regression Equations Showing a Significant Relationship between Denial and D/I, D/O, and Nightly Sleep.

Variable	B	SE B	ß	R^2	ΔR^2	p of ΔR^2	N
Dichotomy/Inside (D/I)							
Step 1				.099	.099	.262	42
Age	.023	.043	.083				
Stage	.185	.239	.107				
Anti-Lipidemic Agents	-3.363	1.348	-.385				
Step 2				.321	.222	.001	
Denial Coping	-.933	.268	-.476*				
Dichotomy/Inside (D/O)							
Step 1				.233	.233	.017	42
Age	-.064	.056	-.159				
Stage	-.143	.335	-.057				
Opiate Agonist Agents	6.791	2.255	.424*				
Step 2				.127	.360	.010	
Denial Coping	1.035	.382	.366*				
Nightly Sleep							
Step 1				.197	.197	.041	41
Age	-.766	.904	-.119				
Stage	7.090	5.218	.191				
Weight	-.683	.245	-.387*				
Step 2				.124	.321	.015	
Denial Coping	-15.831	6.178	-.357*				

* $p < .05$

In a hierarchical regression controlling for age, stage, and opiate agonist medication, the control variables entered on the first step were related to D/O as a group (ΔR^2 = .233; F(3,38) = 3.848, p = .017). Denial entered on the second step independently predicted D/O (ΔR^2 = .127; F(1,37) = 7.348, p = .010), such that denial was associated with a higher D/O (partial r = .407). The entire, four variable model was also significantly associated with D/O (F(4,37) = 5.205, p = .010).

The regression equation with mean nightly sleep as the outcome was significantly predicted by the group of control variables age, stage, and weight (ΔR^2 = .197; F(3,37) = 3.030, p = .041). The subsequent addition of avoidant coping to the model added to its predictive power (ΔR^2 = .124; F(1,36) = 6.567, p = .015), with denial predicting decreased sleep (partial r = -.315). The resulting four variable model explained a significant amount of variance in nightly sleep (F(4,36) = 4.256, p = .006).

Behavioral Disengagement

Hierarchical regression equations were used to investigate the relationship between behavioral disengagement and circadian disruption. In a regression using behavioral disengagement as a predictor of the autocorrelation, control variables included age, stage, and income. The addition of behavioral disengagement on the second step of this equation explained significant variance in the autocorrelation (ΔR^2 = .110; F(1,34) = 5.620, p = .024), with behavioral disengagement being associated with a lower autocorrelation (partial r = -.464), indicating more behavioral disengagement was related to a weaker circadian activity rhythm. The entire, four variable model was also predictive of the autocorrelation (F(3,34) = 4.236, p = .007). Regression equations resulting in a

significant, independent effect of behavioral disengagement on circadian disruption are summarized in Table 14.

Table 14. Summary of Regression Equations with Behavioral Disengagement Coping as a Predictor of Actigraphy Measures of Circadian Disruption.

Variable	B	SE B	ß	R^2	ΔR^2	p of ΔR^2	N
Autocorrelation							
Step 1				.222	.222	.030	39
Age	.002	.002	.134				
Stage	.012	.011	.160				
Income	.032	.015	.338*				
Step 2				.332	.110	.024	
Behavioral Diseng.	-.043	.018	-.373*				
Dichotomy/Inside (D/I)							
Step 1				.099	.099	.262	42
Age	-.001	.043	-.003				
Stage	.317	.243	.184				
Anti-Lipidemic Agents	-3.306	1.334	-.378*				
Step 2				.261	.235	.001	
Behavioral Diseng.	-1.304	.361	-.512*				
Dichotomy/Outside (D/O)							
Step 1				.233	.233	.017	42
Age	-.039	.058	-.097				
Stage	-.284	.344	-.114				
Opiate Agonist Agents	6.760	2.261	.422*				
Step 2				.359	.126	.011	
Behavioral Diseng.	1.405	.522	.382*				

* $p < .05$

In a hierarchical regression exploring behavioral disengagement as a predictor of D/I, control variables included age, stage, and anti-lipidemic medication. The control variables entered on the first step did not significantly predict D/I ($\Delta R^2 = .099$; $F(3,38) = 1.385$, $p = .262$). However, behavioral disengagement entered on the second step

independently predicted D/I (ΔR^2 = .235; F(1,37) = 13.023, p = .001), such that behavioral disengagement was associated with a lower D/I (partial r = -.510), indicating more activity while in bed, likely a sign of circadian disruption. The entire, four variable model was also related to D/I (F(4,37) = 4.623, p = .004).

In a hierarchical regression exploring behavioral disengagement as a predictor of D/O, control variables included age, stage, and opiate agonist medication. The control variables entered on the first step significantly predicted D/O (ΔR^2 = .233; F(3,38) = 3.848, p = .017). Behavioral disengagement entered on the second step also independently predicted D/O (ΔR^2 = .126; F(1,37) = 7.245, p = .011), such that behavioral disengagement was associated with a higher D/O (partial r = .405), indicating more time of diminished activity while out of bed, likely a sign of circadian disruption. The entire, four variable model was also related to D/O (F(4,37) = 5.171, p = .002). No other independent relationships were observed between behavioral disengagement and circadian disruption.

In terms of sleep outcomes, behavioral disengagement was significantly and independently related only to increased time spent awake after sleep onset (ΔR^2 = .096; F(1,38) = 4.179, partial r = .315, p = .048). The covariates, age and stage, were not significantly associated with wake after sleep onset (R^2 = .029; F(2,39) = .592, p = .558). The final, three variable model was also not statistically significant (R^2 = .126; F(3,38) = 1.820, p = .160).

Secondary Analysis #4: Additional Cortisol Measures

To supplement primary analyses with cortisol outcomes, secondary analyses sought to investigate relationships previously tested in primary analyses with the addition of two additional CAR measures: CAR % increase and the area under the awakening curve. The CAR slope was used as the primary CAR outcome measure because it was judged to be a better indicator of the HPA response to awakening as it measures the rate of change from the wake sample to the +30min sample and is not as susceptible to undue influence from extreme awakening values. In addition, analyses of cortisol variables were repeated using the cortisol variables calculated with the awakening values estimated using linear modeling. This was done to minimize the influence of missing values on the cortisol outcomes.

In regression models using the 7-item intrusions scale as a predictor of secondary cortisol outcomes, a hierarchical regression model of the CAR % increase with estimated awakening values included was not significantly predicted by the combination of age and stage ($\Delta R^2 = .051$; $F(2,38) = 1.022$, $p = .370$). However, the addition of the 7-item intrusions scale on the second step significantly explained the CAR % increase ($\Delta R^2 = .102$; $F(1,37) = 4.461$, $p = .041$), with intrusions related to a more dramatic cortisol increase (partial $r = .328$). Other models with the 7-item version of the intrusions subscale as a predictor of secondary cortisol outcomes were not statistically significant. Models testing associations of the 5-item intrusions scale with secondary cortisol outcomes did not reveal and significant, independent relationships.

Intrusions were not significantly and independently related to other CAR measures. This could have been due to the error introduced by the inclusion of estimated

awakening values. In addition, because the awakening cortisol level is the denominator in the calculation of CAR % increase, low awakening values can result in high % increases without a large absolute difference between the awakening and +30min cortisol values.

Exploratory analyses similar to those employed for the evaluation of hypothesis 2 in the primary analyses were repeated with the secondary cortisol outcomes. These correlations can be found in Table 15. The rest/activity autocorrelation was significantly correlated with the area under the awakening curve when estimated awakening values were included (Spearman's r = .338, p = .035). In findings similar to those observed in primary analyses, both the autocorrelation (Spearman's r = -.561, p < .001) and the D/O (Spearman's r = .457, p = .003) were related to the diurnal cortisol slope with the estimated awakening values included. These findings were both such that disrupted activity rhythms were associated with a flatter diurnal cortisol slope. When the number of missing cortisol samples was statistically controlled, significant relationships persisted between the diurnal cortisol slope and both the autocorrelation (partial r = -.578, p < .001) and the D/O (partial r = .401, p = .011).

Table 15. Actigraphy and Secondary Cortisol Variable Correlations (N = 40)

	24 hour Autocorrelation	**Dichotomy Index/Inside**	**Dichotomy Index/Outside**
Waking Cortisol$_{EL}$	.273	.039	-.160
Morning Cortisol Slope$_{EL}$	-.077	-.264	.228
CAR % increase	-.155	-.081	.113
CAR % increase$_{E}$	-.180	-.076	.125
Area under waking curve$_{L}$	.191	.067	-.148
Area under waking curve$_{EL}$	.114	.095	-.136

	24 hour Autocorrelation	Dichotomy Index/Inside	Dichotomy Index/Outside
Diurnal Cortisol Slope$_{EL}$	-.561**	-.273	.457**
Mean diurnal cortisol$_{EL}$	.114	-.176	.194

Legend. "E" subscripts are used to denote summary cortisol variables calculated with the estimated awakening cortisol value included. "L" subscripts are used to denoted cortisol values that are presented after log transformation to correct for non-normal distribution.
All correlations calculated using Spearman's r.
* $p < .05$
** $p < .01$

Secondary Analysis #5: Relationships between Cortisol and Sleep

As a final secondary analysis, the relationships between cortisol and sleep variables were explored. Sleep variables included total nightly sleep, awakenings, wake after sleep onset, sleep efficiency, and sleep onset latency. The effects of daytime and bedtime cortisol on sleep were explored by regressing sleep variables on the mean diurnal cortisol, diurnal cortisol slope, and bedtime cortisol levels with age and stage statistically controlled. In addition, the relationship of sleep to the cortisol awakening response was explored by regressing the mean awakening cortisol, morning slope, % increase, and area under the awakening cortisol curve on each of the sleep variables in separate equations and with age and stage statistically controlled. No statistically significant, independent associations of cortisol and sleep variables emerged from these analyses.

Secondary Analysis #6: Removal of Patients Reporting Depression

Previous literature has noted hypersecretion of cortisol, especially late in the day, in participants reporting depression (Burke et al., 2005). It is possible that, in a

portion of the sample, the hypersecretion associated with symptoms of depression would counteract the diminished secretion of cortisol that could be expected to be associated with intrusions, a symptom consistent with PTSD. To reduce confounding presented by patients reporting high levels of depression, participants scoring more than 1.5 standard deviations above the mean of the standard deviation observed in a standardization sample receiving the POMS were removed from a repeated analysis of circadian cortisol outcomes. Seven participants were removed based on POMS scores. Age and stage were entered on the first step of a hierachical regression equation. Intrusions were entered on the second step. These analyses revealed no significant and independent effects of intrusions on cortisol. Similarly, no effects of the 5-item version of the intrusions measure on cortisol were observed.

DISCUSSION

Summary of Results

This study sought to explore relationships between breast cancer-related intrusions, avoidant coping, and circadian rhythms. Breast cancer-specific intrusions over a four day period between diagnosis and the initiation of treatment were used as an indication of the distress associated with breast cancer. Because detailed investigation of the relationships between intrusions and multiple measures of circadian disruption are not available, an exploratory analytical approach was employed to develop a rich understanding of the data collected and generate hypotheses for future research.

Primary Analyses

Hypothesis 1a: Cancer-related intrusions will be significantly and positively associated with circadian disruption, as measured by salivary cortisol and actigraphy.

Analyses of the relationship between intrusions and circadian disruption revealed that intrusions were significantly related to a lower autocorrelation coefficient for rest/activity rhythms. These effects were independent of the effects of two theoretically-derived control variables, age at diagnosis and cancer stage, as well as one empirically-derived variable, income. This effect persisted when items from the IES intrusions scale that discussed sleep were removed. Intrusions were not independently related to the dichotomy indices of activity while in bed and while out of bed.

Intrusions were also related to an increased CAR % increase, possibly indicating an exaggerated response of the HPA to awakening. There is no consensus interpretation of the cortisol awakening response, so the implications of these findings are not clear. An elevated CAR% increase might be the result of an absent pre-awakening cortisol rise characteristic of circadian disrupiton. Because this was a naturalistic study, assessment of pre-awakening cortisol levels that have been performed in a laboratory setting were unavailable. As a result, the association of intrusions with increased CAR % increase is consistent with circadian disruption due to an absent pre-awakening cortisol rise, and a pre-awakening cortisol rise is hypothesized as a mechanism, but this explanation cannot be confirmed based on the data available in the current study. Further, an increased CAR % increase could be indicative of stress appraisals in the morning, meaning such a result could be interpreted as being consistent with circadian rhythmicity. Evidence of a relationship between intrusions and circadian disruption is of clinical relevance for several reasons. Significant levels of intrusion have been reported in 36% of patients after receiving a diagnosis of breast cancer (Green, Rowland, & Krupnick, 2000), indicating that this is a symptom experienced by a large number of patients. Any relationship of intrusions with circadian disruption would apply to a notable proportion of patients who have breast cancer. In light of studies identifying circadian disruption as a predictor of shortened survival (Mormont et al., 2000; Sephton et al., 2000), it is clinically relevant to note that distress, specifically intrusions, associated with the diagnosis of breast cancer may also be related to circadian disruption.

It is interesting to note a possible relationship between intrusions and circadian disruption was largely limited to the autocorrelation coefficient, especially in light of

studies reporting a significant association of intrusions with cortisol (Dettenborn, 2006). To date, most of the studies of intrusions and cortisol have investigated the overall cortisol over a period of time, as opposed the circadian rhythmicity variables employed in this study. An alteration in total output would not necessarily be reflected in measures of circadian rhythmicity. However, the overall mean cortisol level was evaluated in this study, and intrusions did not exhibit a significant association with this measure or with log-transformed awakening and bedtime cortisol values.

The notion of allostatic load proposed by McEwen (McEwen & Stellar, 1993) is a useful conceptual model for the disruption of endocrine functioning, including cortisol. This model proposes that physiological adaptations to stress can take a toll on body systems over time. The wear and tear of allostatic load that could result in disrupted circadian rhythms may take place over a number of years. In this study, women had been informed of their diagnosis of breast cancer recently, often on the same day as their enrollment in the study. The physiological effects of stress may not have been observed because these effects simply do not appear in response to stressors unless exposure to these stressors persists over a long period of time. In fact, it has been argued that brief, intermittent stressors present a challenge that promotes a healthy adaptation by the individual (Epel & McEwen, 1998). Studies of circadian cortisol rhythms have reported notable interdaily instability, suggesting that circadian rhythms are sensitive to environmental and psychological stress. As a result, it is reasonable to expect that a diagnosis of breast cancer would induce sufficient distress to alter circadian cortisol rhythms. Still, changes in circadian cortisol rhythms may be attributable to influences other than psychological distress, such as medications, diet, or exercise.

In light of other possible explanations, interdaily variability in circadian cortisol rhythms does not necessarily mean that these rhythms are sensitive to changes to intrusions, the specific measure of psychological distress used here, but distress-induced disruption is evident from other studies. It is hypothesized that a longitudinal study of women with breast cancer would observe that post-diagnostic distress would be predictive of later development of disrupted circadian cortisol rhythms. The finding that post-diagnostic intrusions were more closely associated with disrupted rest/activity rhythms than with cortisol rhythms suggests a new explanation for disrupted circadian cortisol rhythms. It is possible that disrupted rest/activity rhythms mediate the relationship between distress and circadian cortisol rhythm disruption. This model hypothesizes that disrupted rest/activity rhythms would predict subsequent disruption of circadian cortisol rhythms in longitudinal studies of women with breast cancer.

A larger sample size would be needed to appropriately test a more complex model of the relationships between stress, coping, and adaptation. Future research in a larger data set could include a self-report assessment of the degree to which patients perceived the relevant event as stressful. Although a diagnosis of breast cancer is likely deemed stressful by most patients (Rowland, 1998), the degree to which someone appraises the illness as stressful varies, and this variable is also of significance to the model that guided the design of the current study.

Distress was measured by the IES intrusions scale in this study because studies have noted that intrusions are prevalent (Jacobsen et al., 1998) and predictive of long-term distress in patients with breast cancer (Bleiker et al., 2000). This measure also allowed assessment that was explicitly tied to the diagnosis of breast cancer, as opposed

to general distress. Future studies might benefit from a measure of general distress that would assess the influence of breast cancer, or another stressor, or generalized distress as well as measuring the influence of other significant stressors in the lives of people that suffer from breast cancer. It is hypothesized that breast cancer-related intrusions would be most strongly associated with post-diagnostic circadian disruption but that other measures of distress would also exhibit modest associations with circadian disruption.

A number of studies employing daily assessments have measured dynamic processes over many days (Tennen & Affleck, 1996). Daily assessments over a longer period of time allow within-person daily fluctuations to be analyzed using advanced statistical techniques (Tennen, 2000). These studies are not well matched for studies that are conducted within a brief time window, such as between cancer diagnosis and treatment, but patients could be followed throughout the course of long-term treatment or during the remission phase of breast cancer. Alternatively, patients could be assessed across several phases of diagnosis and treatment. Collection of daily assessments over a longer time period would allow within-subjects statistical testing, using more advanced statistical methods such as hierarchical linear modeling. These techniques would likely be more sensitive to detecting the relationships hypothesized in this study. It is hypothesized that data collection allowing for use of advanced statistical techniques would reveal stronger relationships between intrusions and circadian disruption and would more effectively discriminate between measures of circadian disruption that are affected by intrusions and those that may be independent from distress.

The aim of capturing quickly changing phenomena closer to the time of their occurrence is furthered by daily assessments, but a time lag between appraisals made,

coping efforts undertaken, and intrusions experienced remains. Assessments could be placed closer to the time of their occurrence using ecological momentary assessment, devices that prompt participants to respond immediately regarding psychological phenomena. Participants in this study wore actigraphy devices throughout the day and reported little difficulty or obtrusiveness related to actigraphy devices, so it is possible that these devices could be supplemented or replaced by other unobtrusive devices. These devices differ in that actigraphy devices require no maintenance, other than removal in situations in which they are likely to get wet. Despite the cost of using ecological momentary assessment devices, based on the results observed in the current preliminary study, the use of more resources to extend these findings may be merited. It is hypothesized that utilization of devices that allow psychosocial phenomena to be captured closer to their occurrence would provide more valid assessments and more sensitive tests that would reveal stronger relationships between intrusions and circadian disruption.

Because this was an exploratory study, this finding is preliminary, and it was not observed with other actigraphy variables or with circadian cortisol rhythms, replication is essential. Based on this study, it is hypothesized that breast cancer-related intrusions would be related to disrupted rest/activity rhythms, but not necessarily to physiological rhythms, in the period immediately following diagnosis. Replication of a relationship between intrusions and disrupted rest/activity rhythms as well as extension of these findings in a longitudinal study, would support the importance of available resources and intervention to address distress associated with a breast cancer diagnosis. It is important to address this distress primarily because of the clinical relevance of distress as a clinical

outcome. However, an association of intrusions with the rest/activity autocorrelation, a variable predictive of survival in one study (Mormont et al., 2000), would suggest the possible presence of poor physical health outcomes influenced by intrusion levels.

Hypothesis 1b: Avoidance as a moderator of intrusion and circadian disruption

The relationship between intrusions and autocorrelation was carried forward to a test of avoidant coping as a possible moderator of this relationship. Tests using the overall avoidant coping score as well as the self-distraction, denial, and behavioral disengagement subscales revealed no significant moderation of the effect of intrusions on circadian rhythms.

The lack of moderation is reasonable given the low statistical power for tests with an interaction term and the modest sample size for this study. Considering the modest relationships often observed between psychosocial variables and physiological variables, a number of factors could explain the lack of a moderation finding. In addition, the intrusions and avoidant coping predictors were moderately correlated (Pearson's $r = .554$, $p < .001$), compromising the interpretability of the interaction term. Baron & Kenny (1986) indicated that these conditions are not ideal for testing moderation effects. This correlation may have influenced the absence of a finding with the interaction term tested in this model.

The transactional model illustrated in the introduction places the appraisal of threat, harm, or challenge before the onset of coping and distress (Lazarus, 1984). Based on this conceptualization, it might be expected that coping could moderate the effects of perceived stress on the resulting distress but can not moderate the effects of distress on

physiology or behavior. However, the transactional character of the model means that the variables interact extensively with one another. Lazarus (2000) has emphasized the potential for any of these variables to act as predictors, moderators, and outcomes and has called for richer investigation of the interrelationships between these variables. In keeping with that goal, this study investigated avoidant coping both as a moderator and as a predictor in models exploring circadian disruption.

It should also be noted that the stress, coping, and adaptation process renews as distress continues and stressors persist. Thus, even if coping initially precedes distress in response to the first exposure to a stressor, it is likely that coping will also follow distress and influence the effects of distress on variables such as the physiology, sleep, and rest/activity rhythms explored in this study. The figure illustrating the transactional model of stress, coping and adaptation is shown on page 19. Still, it is interesting to note that avoidant coping was predictive of circadian disruption when it was specified as a predictor but not when it was specified as a moderator in models in this study.

Hypothesis 2: Diurnal salivary cortisol slope and rest-activity rhythm obtained by actigraphy will be significantly and positively associated.

One of the strengths of this study is the use of multiple measures of circadian rhythmicity. Consequently, exploration of the type and strength of the relationship between these two measures is of interest. Generally, the expected relationships were evident. A higher 24-hour autocorrelation generated from actigraphy data was related to a steeper diurnal decrease in the cortisol slope. The relationship between these measures suggests they will yield similar indications concerning circadian rhythmicity. The

autocorrelation was related to a lower bedtime cortisol level, a result that is consistent with stronger circadian rhythmicity, as cortisol is typically at its nadir in the evening. This finding informs comparison of the two studies reporting that circadian rhythms were predictive of cancer survival because one study used the rest/activity autocorrelation (Mormont et al. 2000), and the other study used the diurnal cortisol slope (Sephton et al., 2000). Preliminary evidence from the current study suggests these two variables measure similar phenomena, as they were moderately to highly correlated in a sample of women with breast cancer in this study. The correlation in this study ($r = -.614$) was such that there appears to be a meaningful amount of independent variance between the rest/activity autocorrelation and the diurnal cortisol slope, indicating that the inclusion of multiple measures of circadian disruption would be a useful methodological characteristic of future studies.

More frequent activity while in bed (D/I) was related to a flattened diurnal cortisol slope in this sample, the sole significant, independent relationship of D/I with a primary cortisol outcome. Because D/I is a measure of activity while in bed, typically at night, it is interesting that D/I would be related to the diurnal decrease in cortisol. Due to their proximity to getting into and out of bed, it might be expected that bedtime cortisol or CAR variables would be more strongly associated with D/I. Due to the small sample size of this study, relationships of D/I with CAR and bedtime cortisol cannot be discounted, but they were not evident in the current sample.

The relationship of D/I to the diurnal cortisol slope is interpretable in that they are both taken to be indicators of circadian disruption. It is interesting to note that inactivity while out of bed (D/O) was also related to a flattened diurnal cortisol slope, meaning all

of the actigraphy measures of circadian rhythms were related, in the expected direction, to the diurnal cortisol slope. This lends further support to the comparability of these two measures and the utility of the diurnal cortisol slope in characterizing circadian rhythms. While abnormality in a given measure of circadian rhythmicity is noteworthy, weak circadian rhythms would theoretically be expected to be evident in disrupted rhythmicity throughout the day. The relationship between the diurnal cortisol slope and an overnight measure of circadian disruption (D/I) is consistent with the idea of a stable circadian rhythm, rather then transitory disruptions. Based on the robust relationship of the diurnal cortisol slope with measures of circadian disruption obtained using a different modality, actigraphy in this study, it is hypothesized that the diurnal cortisol slope would be related to other indicators of circadian rhythmicity such as body temperature and brain wave activity.

A higher D/O was also associated with higher bedtime cortisol levels. It is noteworthy that frequent inactivity while out of bed is related to increased cortisol levels in the bedtime. It might be expected that increased availability of glucose would be related more activity, so this relationship is in need of further exploration. Conceptualized from the perspective of circadian rhythms, inactivity during the day and elevated bedtime cortisol levels are consistent with circadian disruption. In this case, circadian disruption offers an explanation for a relationship that is otherwise counterintuitive, suggesting that circadian rhythms are an important tool in understanding activity and physiology in patients with breast cancer.

Finally, a higher D/O was related to a steeper morning cortisol slope. It is interesting to note that frequent inactivity while out of bed is correlated with increased

cortisol availability in saliva in the morning, similar to the results observed between D/O and the bedtime cortisol level. A stronger CAR might otherwise be interpreted as a mobilization of physiological resources for daytime activity, but these patients ultimately exhibited decreased activity as indicated by the D/O. This could be explained by the absence of a pre-awakening cortisol rise in patients with disrupted circadian rhythms, and that a subsequent spike in post-awakening cortisol secretion was then observed.It is possible that psychological states, such as stress appraisals, could have elevated cortisol levels in the morning, though the intrusions measure employed in this study was not related to the CAR measures. It is reasonable to hypothesize that future studies measuring stress perceptions or additional measures of distress might find a relationship between psychological states and the CAR in women with breast cancer. As with other associations between measures of circadian disruption, the correlation between D/O and the morning cortisol slope could be explained by their conceptual link as measures of circadian rhythms.

Findings of a relationship between actigraphy and cortisol measures of circadian rhythmicity are consistent with a study of patients with metastatic colorectal cancer noting that patients within the upper quartile of the rest/activity autocorrelation had a higher ratio of 8 a.m. to 4 p.m. serum cortisol samples than patients in the lower quartile of the rest/activity autocorrelation (Rich et al., 2005). Similar to the results presented in the current study, patients in the Rich et al., (2005) study also exhibited no relationship between the autocorrelation and mean diurnal cortisol levels. The rest/activity autocorrelation was also related to the difference between 8 a.m. and 4 p.m. serum cortisol levels in a previous report on this sample of patients with metastatic colorectal

cancer patients (Mormont et al., 2000). Similarities in the findings of the current study and that of Rich et al. (2005) are noteworthy because of significant differences in methods, including serum vs. salivary cortisol assessment, different calculations of the cortisol rhythm, and differences in cancer site and timing within the disease course.

Overall, the data presented in this study support the conceptualization of these two measures as circadian rhythms. Nevertheless, correlations between these two measures were typically moderate, suggesting that while there is considerable conceptual overlap between the two measures, they also provide unique data when used concurrently.

Secondary Analyses

To further the aim of hypothesis generation that is essential to exploratory data analysis, secondary analyses were conducted. These analyses explored additional relationships among major study variables.

Sleep Outcomes

Sleep variables calculated from rest/activity data were examined as outcomes with the same analysis plan as that used for the examination of other circadian rhythm variables for hypothesis 1a. Sleep is a process characterized by the lack of consciousness, presenting an obvious barrier to self-report as an assessment method. Consequently, the availability of an alternative measure of sleep through actigraphy is valuable.

Intrusions were not significantly associated with sleep outcomes in any of the regression models employed. This result contradicts recent research suggesting a

significant relationship between the distress associated with breast cancer and sleep disturbance in women receiving chemotherapy (Roscoe et al., 2007) and in another sample of women with metastatic breast cancer (Palesh et al., 2007). However, caution is merited due to the small sample size. While intrusions were not related to sleep disturbance in this sample, other measures of distress may influence sleep, including depression (Palesh et al., 2007). In addition, the sample from the current study was not receiving treatment and most of the patients did not have metastatic disease. It is possible that these factors in particular accounted for the sleep disturbance observed in previous studies of women with breast cancer and explain the absence of findings in the current study.

Each morning, participants completed a questionnaire assessing the prior night's sleep and actiwatch removals. The final question invited participants to provide qualitative data on their sleep, and stated "do you have any other comments regarding last night's sleep". Selected comments regarding the cancer diagnosis and sleep are presented below.

"I couldn't stop thinking - so much was taking in a day and still not understanding if there will be a tomorrow"

"nightmares about dying"

"first time to dream about cancer"

"just before sleep is when I have a deep sense of facing my mortality and dealing with the prospect of physical pain to come"

"Kept coughing, had to get up and get drink. Kept worrying about that. Mind started racing that cancer had spread to lungs"

"Dreamed about reading to make decision on type of cancer surgery"

Qualitative data provide detailed self-reports regarding sleep. The statements about intrusions regarding the diagnosis and treatment of breast cancer that appear immediately prior to sleep suggest that these are relevant to the intrusions construct and that it is important to include items that discuss sleep in the 7-item version of the IES intrusions scale, as opposed to the 5-item version suggested by a more recent factor analysis (Witteveen, 2006). In addition to breast cancer-related thoughts and dreams, other life stressors and dreams were reported in response to the question about the prior night's sleep. It is important to keep in mind that although a diagnosis of breast cancer is often a source of significant distress, pre-existing and co-occurring life stressors certainly contribute to elevated distress. These sources of distress were not targeted by the intrusions measure employed in this study. It follows that the absence of a significant relationship between intrusions and sleep in this study does not rule out the possibility that general distress was related to sleep disturbance in these patients.

Direct Effects of Avoidant Coping on Circadian Disruption

The transactional model of stress, coping, and adaptation allows for a number of relationships among these variables (Lazarus, 2000), so avoidant coping was investigated as a predictor of circadian disruption in an exploratory analysis. The analytical approach for the evaluation of avoidant coping was similar to the one employed in the evaluation of intrusions as a predictor in hypothesis 1a. In addition to the summary score for avoidant coping, the self-distraction, denial, and behavioral disengagement subscales of the avoidant coping measure were investigated as predictors of circadian disruption.

The summary avoidant coping score was related to a lower autocorrelation, an indication of circadian disruption. In follow-up analyses of the avoidant coping subscales, only behavioral disengagement was significantly and independently related to the autocorrelation, suggesting behavioral manifestations of avoidance have the most direct influence on disruptions in the circadian activity rhythms. This finding is intuitive in that activity levels are a behavioral variable as well, but the items of the behavioral disengagement scale of the brief COPE does not refer to inactivity specifically. Rather, the items refer to "giving up trying to deal with it" and "giving up the attempt to cope", which could possibly be interpreted as giving up cognitive and emotional coping efforts in addition to behavioral efforts.

Avoidant coping is often characterized as a maladaptive way of coping with a stressor, but it could alternatively be conceptualized as an adaptive means of maintaining a life that is as normal as possible in spite of the stressor. This might be especially useful over a short period of time. In the current sample, this did not appear to be the case, as avoidant coping was related to disrupted rest/activity rhythms, suggesting that avoidant coping failed to eliminate the stressor from awareness or failed to ameliorate the effects of the stressor in terms of circadian rhythmicity. This informs models of avoidant coping and contributes to a substantial literature linking avoidant coping with undesirable outcomes. If further research supports the conceptualization of avoidant coping as predictive of circadian disruption and other clinically relevant adverse outcomes, coping techniques such as distraction could be viewed as potentially problematic, even during short-term efforts to cope with a breast cancer diagnosis. Results suggesting avoidant coping has an effect on a measure of circadian rhythmicity support conceptualization of

influences of avoidant coping on circadian disruption, as opposed to models proposing avoidant coping as a moderator of the effects of stress or intrusions on circadian disruption.

In the model testing avoidant coping as a moderator of the association of intrusions with the rest/activity autocorrelation, the mean-centered avoidant coping variable entered as a covariate on the first step was significantly related to the rest/activity autocorrelation. This is consistent with the significant association of avoidant coping with a lower rest/activity autocorrelation observed in secondary analyses.

Avoidant coping was also related to more frequent high activity levels during time spent in bed (D/I). Subsequent analyses of individual subscales of the COPE revealed that the denial and behavioral disengagement subscales of this measure were related to circadian disruption indicated by D/I, but the self-distraction subscale was not. While avoidant coping was related to high activity levels in the time spent in bed, it is surprising that avoidant coping was not related to sleep variables in this sample. Consistent with the interpretations of other similar findings in this dataset, this finding may be taken as support for the distinction between general circadian disruption and sleep, which accounts for part of the circadian rhythm.

Although many of the analyses exploring relationships between avoidant coping and circadian disruption did not result in significant, independent associations, no analyses revealed a relationship between avoidant coping and improved circadian rhythmicity. It follows that this study's results suggest any link between avoidant coping and circadian disruption is limited, but negative to the extent that a relationship exists. There are several possible clinical implications of these results. Primarily, they are

consistent with the idea of offering psychological treatment, emotional support, and medical and psychosocial information. It is likely ill-advised to restrict a patient's autonomy by pressuring the patient to adopt a given view or coping style, but promoting awareness of available resources might encourage engagement of the stressor without carrying a negative connotation for the patient. Fears about interfering with avoidant coping strategies that are successful for short-term coping are not furthered by the results of the current study. In addition, within the limits of the circadian disruption outcome investigated by this study, increased availability of outlets for expression, overt discussion of matters related to the breast cancer diagnosis, and treatment of distress makes sense in terms of health care policy.

Although there were no other analyses revealing an association of the summary avoidant coping score with measures of circadian disruption that was independent of the covariates in this study, additional analyses explored relationships of avoidant coping subscales with circadian disruption. Elevation of the self-distraction subscale was independently related to an increase in a secondary cortisol outcome, the area under the awakening cortisol curve, a finding that was not observed with either of the other two avoidant coping subscales. This finding remained when awakening values estimated using linear modeling were included. Perhaps not coincidentally, elevation of the self-distraction subscale was also independently related to a higher awakening cortisol level. This finding was also not altered by the inclusion of estimated awakening values.

In considering the CAR, the pattern of findings observed with self-distraction offers further insight. Because the area under the awakening cortisol curve includes the awakening and 30 minute post-awakening values, an elevated awakening cortisol value

has a heavy influence on the area under the awakening cortisol curve, even if the post-awakening increase is not dramatic. The lack of a significant, independent relationship between self-distraction and the other two CAR measures, slope and % increase, suggests that the increased area under the awakening curve was primarily driven by elevated awakening values. As a result, it is not hypothesized that self-distraction would be related to CAR in future studies of women with breast cancer studied between the times of diagnosis and initiation of treatment. However, relationships with the awakening cortisol level would be hypothesized to be evident. Because the interpretation of the CAR as it relates to self-distraction is not straightforward, it would be interesting to note the longitudinal effects of an elevated awakening cortisol level during the post-diagnostic period. A study designed to test whether post-diagnostic awakening cortisol levels are predictive of subsequent indicators of circadian disruption would be useful in clarifying the interpretation of awakening cortisol levels in women with breast cancer. Until studies like these are conducted, the clinical implications of this finding are unclear.

The denial and behavioral disengagement subscale of the avoidant coping measure were independently related to increased D/O, meaning these patients exhibited more time out of bed in which activity levels fell below the median activity levels for time in bed. This is likely an indicator of disrupted circadian activity rhythms. In support of this inference, a higher D/O was related to cortisol measures of circadian disruption, including a more dramatic increase in the morning cortisol slope, a flattened diurnal cortisol slope, and elevated bedtime cortisol levels. It is perhaps unsurprising that self-distraction was not related to daytime inactivity, as self-distraction is consistent with activity during waking hours that might occupy the patient and divert attention from

reminders of breast cancer. It is possible that patients attempt to avoid reminders of breast cancer by restricting activities that might bring them into contact with other people who might ask about their health condition or experience reduced enjoyment of activities due to distress, especially cancer-related intrusions. It is hypothesized that these factors would be evident in studies designed to assess them. This finding may offer preliminary support for interventions increasing exercised for women with breast cancer, as daytime activity could be particularly sensitive to avoidant coping in response to the cancer diagnosis.

In terms of sleep outcomes, a model of denial as a predictor of decreased nightly sleep. Additionally, behavioral disengagement was related to increased time spent awake after sleep onset. It is possible that cognitive avoidance strategies are more difficult to enact when patients try to go to sleep because their attention is not taken up by other activities. Consistent with findings in other analyses from this study, psychosocial factors appeared to be more strongly related to circadian rhythms generally, as opposed to sleep specifically. To the extent that denial is related to nightly sleep, ready availability of resources and treatments that encourage engagement of stressors and expression regarding the diagnosis of breast cancer may be supported. Brief behavioral treatments and medications for addressing sleep problems are available, and these treatments may promote improved circadian rhythmicity. Future research could utilize ecological momentary assessment or brief questionnaires in the morning to assess the content of thoughts experienced by women with breast cancer as they go to bed. It is hypothesized that attempts to avoid or deny the presence of breast cancer would be linked with sleep disruption.

In modeling the variables studied, the cross-sectional nature of the study inhibits causal inferences. Therefore, relationships between avoidant coping and circadian disruption may both be caused by a third variable not included in analyses. The pathophysiological processes associated with cancer are one possibility. This potential confound was addressed by including cancer stage as a covariate in analyses. Nevertheless, cancer stage as an estimate of disease severity may not fully capture the physiological processes affecting psychosocial variables such as intrusions and avoidant coping as well as circadian variables as indicated by actigraphy and cortisol. This study also emphasized generalizability in applying relatively few exclusion criteria. However, future studies might consider eliminating other potential confounds such as substance abuse problems and psychological and medical diagnoses by conducting diagnostic interviews or controlling for them statistically.

Longitudinal studies that begin at the time of initial breast cancer screening, such as at the time of the mammogram, could track avoidant coping and circadian disruption over time and contribute to understanding of whether avoidant coping precedes the development of circadian disruption or speak to the possibility of the opposite temporal relationship.

Secondary Cortisol Outcomes

In testing secondary cortisol outcomes, the seven item versions of the intrusions subscale of the IES predicted increased CAR %. Ambiguities in CAR interpretation reviewed above do not permit strong conclusions to be draw from this finding. In addition, when awakening values estimated using linear modeling replaced values that

were missing due to nonadherence to the protocol, intrusions were not related to CAR %. Finally, no other CAR outcomes were significantly and independently associated with intrusions. Despite these limits, a relationship between intrusions and a higher CAR % is consistent with an interpretation of a more dramatic CAR as an indicator of distress. Given the association of psychosocial stressors, including PTSD, with a diminished CAR, it is certainly possible that an increased CAR indicates a healthy response of the HPA axis. At this point, it seems reasonable to hypothesize that the CAR would be interpreted differently depending on sample and situational characteristics.

Aside from interpretation issues, it is noteworthy that previous research has reported a relationship between PTSD and a diminished CAR (Rohleder, Joksimovic, Wolf, & Kirschbaum, 2004). It should be noted that intrusions are only one part of PTSD, so elevated intrusions can not be equated with PTSD. This distinction is especially relevant to the current sample, in which participants provided data shortly after being confronted with the stressor of being diagnosed with breast cancer. As a result, the observed results are in line with expectations. It is possible that the heightened cortisol in response to awakening associated with cancer-specific intrusions in this study were part of responsivity in the acute phase of coping with a stressor.

In repeats of hypothesis 2 using secondary cortisol outcomes, an elevated rest/activity autocorrelation was related to increased area under the awakening cortisol curve, but only when estimated awakening cortisol values were included in the calculation. Cautious interpretation of this finding is needed because it was only observed with estimated awakening values included. In this analysis, a more exaggerated CAR is related to a measure indicating increased circadian rhythmicity, adding to the difficulty

interpreting CAR findings. Longitudinal investigations into the outcomes predicted by CAR variables would improve the interpretability of these results. Longitudinal studies could also note relationships of CAR variables with other indicators of circadian rhythms over time.

A higher rest/activity autocorrelation was related to a steeper diurnal cortisol decline with estimated awakening values included. This is consistent with a finding linking these two variables in hypotheses two analyses with no estimated awakening values. An increased D/O, meaning more frequent inactivity during the day, was related to a flatter diurnal cortisol slope with estimated awakening values included. This was also consistent with results obtained in testing of primary cortisol outcomes in hypothesis two analyses. These findings add to the robustness of the relationships between these variables but do not alter the interpretation.

Cortisol and Sleep

Secondary analyses of the association between cortisol and sleep revealed no significant, independent associations of circadian cortisol variables and sleep outcomes. Because sleep is a component of circadian rhythms, it is surprising that circadian cortisol variables and sleep outcomes would not be related more strongly. However, because type II error is a clear possibility in a small sample, retention of the null hypothesis is in need of cautious interpretation. It is hypothesized that in larger data sets, relationships among more of the measures of circadian rhythms would be observed, based on their overt conceptual links. Still, other interpretations are possible. There is a meaningful distinction between 24-hour rhythms and sleep. Disrupted circadian rhythms may not ultimately

manifest in sleep disturbance. The SCN is crucial in the regulation of circadian rhythms, but sleep outcomes are influenced by a number of other variables, ranging from behavioral variables targeted by sleep hygiene interventions to physiological variables such as melatonin secretion.

Depression as a Potential Confound

The final of the secondary analyses sought to determine whether the effects of depression influenced results obtained in previous analyses. Patients were removed from analysis based on elevated scores on the depression subscale of the POMS, and procedures employed in hypothesis 1a were repeated. No significant relationships emerged from these analyses, possibly because the elimination of eight additional participants limited the statistical power of an already small sample. Nevertheless, no support was found for the notion that depression masked relationships in previous analyses.

Strengths and Limitations

Multiple Measures of Circadian Disruption

Data collection for this study allowed for extensive analysis of two measures of circadian disruption. Measures of physiological rhythms and activity rhythms, as well as sleep assessment that did not rely on self-reported sleep, yielded interesting and surprising results. Detailed analysis of multiple measures of circadian disruption sheds some light on previous studies using different measures. Circadian disruption has been predictive of cancer survival in two studies, but circadian rhythms have been measured

with the diurnal cortisol slope (Sephton et al., 2000) and the 24-hour rest/actigraphy autocorrelation yielded by actigraphy (Mormont et al., 2000). This is of particular interest in cancer patients because circadian disruption can take many forms in this population and increases with advanced illness. As a result, different measurement modalities may be needed to fully capture the circadian disruption in cancer patients, and multiple types of circadian disruption may need to be assessed.

Although it would be reasonable to speculate that measures of circadian disruption would be associated, this hypothesis has not previously been formally tested. As a result, the degree of concordance of these two findings in cancer patients, for whom extensive dysregulation of circadian rhythms is evident, was unknown. Results from this study indicate that these measures are related and in the expected direction. In light of this finding, the idea that circadian disruption is a conceptual variable linking the diurnal cortisol slope and rest/activity rhythm is supported. Circadian disruption can reasonably be proposed as predictive of survival in two studies of patients with cancer.

Data on Homogeneous Group of Women

Generalization from these data are limited by the homogeneity of the sample in that all participants were diagnosed with breast cancer of various stages and were between the time of diagnosis and the initiation of treatment. These results may not generalize to patients during the diagnostic testing, treatment, or post-treatment remission phases of cancer. Results may have also have limited applicability to men and patients suffering from cancer at other bodily sites. There was substantial diversity in race within

this sample, as only 55% of the sample was Caucasian, so generalizability of results is not expected to be limited to one racial group.

The common timing with respect to diagnosis, in particular, is not frequently seen in studies of psychosocial aspects of patients' experience of cancer. Because reactions to cancer are likely to vary over time, patient similarities in the course of diagnosis and treatment reduce variance in the illness as a stressor for participants in this study. However, the stressors that patients are experiencing at the time of diagnosis, or that confront patients during data collection, could not be held constant and likely influence patients' stress levels, intrusions, and possibly circadian rhythms.

Patients that enrolled in this study had recently been diagnosed with cancer and were anticipating treatment. Many were likely considering several treatment options and experiencing significant time constraints. As a result, coping, intrusions, and activity rhythms were expected to change rapidly. Because of these features of the sample, multiple assessments were deemed worthwhile to increase the reliability of self-report variables, a practice that is commonly employed in assessments of circadian cortisol rhythms. The collection of daily self-reports also promoted concordance among the spans of time over which data were collected for cortisol, actigraphy, and self-report data. While daily assessments are appealing from a conceptual perspective, results may have limited generalizability to trait-oriented measures of intrusions and coping.

Sample Size

Collection of detailed data in a specific sample within a brief time window has the potential to limit accrual. In this study, a total of 44 participants enrolled and provided

enough data to be included in some analyses. Possibly due to the demands of being recently diagnosed with cancer, complete data could not be collected for all participants. The saliva samples that were missing, insufficient for assay, or collected outside the specified time window presented a threat to validity to the extent that they might have been missing in a nonrandom pattern. Analyses attempted to adjust for this problem by controlling for the number of missing samples with the diurnal slope or bedtime cortisol level as an outcome because the number of missing samples was correlated with these outcomes.

While the sample size was expected to provide sufficient statistical power to detect the effects proposed for primary analyses, the sample size was relatively small. This small sample size likely limited the ability of this study to detect effect sizes in some of the secondary analyses. The limits of a small sample size were ameliorated somewhat because the study was exploratory in nature in an effort to capitalize on the rich data provided by patients who participated in this study. None of the results from this study are intended to present confirmatory conclusions regarding population relationships among study variables. Relationships that were not statistically significant in this analysis should not be discounted. The small sample size should also be considered in evaluating relationships that were not statistically significant.

Comments and Implications

Because this was an exploratory study, the results observed do not determine whether the relationships exist, but rather indicate the types of relationships that are particularly interesting for more focused, confirmatory studies. Daily assessments of

intrusions and avoidant coping prompted participants to tie responses to the experience of having breast cancer, meaning the effects of psychosocial variables on circiadian disruption are conceptually tied to the stress of breast cancer diagnosis specifically. Daily psychosocial assessments at the same time as physiological and activity data collection also allowed for increased reliability through multiple assessments.

Actigraphy and cortisol measures of circadian rhythmicity are likely to provide unique variance simply as a function of the mode of assessment. While actigraphy assesses rest/activity behavior, cortisol provides information on physiological rhythms. They might also be expected to be distinct because cortisol rhythms are so responsive to the regulation of the SCN. Rest/activity rhythms are almost certainly influenced by the SCN, but they are also likely to be more responsive to fluctuations in daily occupational, social, and recreation routines. It was interesting to note that a relationship between circadian cortisol rhythms and sleep was often absent in this sample, but sleep is clearly altered if environmental factors such as noise or the availability of appealing activities is strong. Aside from environmental factors, cognitions often alter sleep outcomes, as well as rest/activity pattern. Perhaps biofeedback could allow someone to learn to exert a degree of conscious influence on cortisol secretion, but sleep can reliably be intentionally delayed, and an individual can transition from rest to activity almost effortlessly. In this way, it makes sense to conceptualize rest/activity circadian rhythms as being influenced by a fairly balanced contribution of endogenous, exogenous, and psychological factors. In contrast, circadian cortisol rhythms, while certainly influenced by exogenous and psychological factors, are more often determined by endogenous rhythms.

The unique variance in circadian rhythms provided by dual assessment of actigraphy and cortisol is clearly useful in a study of primarily circadian rhythms, but these measures may be differentially effective depending on the aim of the study. For instance, a study of the influence of rhythms on cancer incidence or survival might favor collection of cortisol rhythms if only one measure of circadian rhythmicity could be completed, as cortisol is expected to be more closely linked with biology. However, a study of the influence of psychological or behavioral variables on circadian disruption might favor the use of actigraphy as a measure of circadian rhythms because rest/activity patterns are expected to be more closely related to psychosocial variables.

There are also clinical reasons for determining which circadian rhythm measure to use if only one can be chosen. The study of rest/activity rhythms could be more useful in the context of psychosocial interventions because these rhythms could be directly addressed by cognitive-behavioral interventions. These could include established interventions targeting behavioral activation and sleep hygiene treatments, as well as other interventions that could easily be developed with the aim of producing more reliable circadian rest/activity rhythms. Given the results of the current study, rest/activity rhythms might be of more interest to studies of patients early in the course of disease. Cortisol rhythms could be of interest to studies aiming to develop better medical intervention such as chronomodulated chemotherapy or medications addressing cortisol irregularities associated with cancer.

In speculating that psychosocial variables are more strongly related with rest/activity rhythms and cortisol rhythms are more strongly related to biological outcomes, a larger model can also be conceived. The disruption of circadian cortisol

rhythms by psychosocial variables may be mediated by rest/activity rhythm disruption. The results from the current study are consistent with this conceptualization, as intrusions were related to disrupted rest/activity rhythms, but few relationships with disrupted cortisol rhythms were observed. As this study included only women who had been recently diagnosed with breast cancer, perhaps disruption of the cortisol rhythm would be present only after prolonged exposure to abnormal rest/activity patterns.

The reason rest/activity rhythms might influence subsequent disruption of circadian cortisol rhythms is not known, but several possibilities exist. One possibility is that the body might adjust to disrupted rest/activity rhythms with less pronounced physiological rhythms as a means of adaptation to environmental demands. Strong circadian cortisol rhythms are less useful if physiological resources are not reliably needed at specific times of the day, but are rather needed sporadically throughout the day and night. Another possibility is suggested by epidemiological studies of cancer incidence in people working third shifts. Decreased melatonin secretion has often been proposed as a mechanism for this effect because melatonin suppresses estrogen and increased exposure to estrogen is a risk factor for breast cancer. People who work third shift are exposed to light at night more often than people who sleep at night, and this light inhibits secretion of melatonin. Similarly, people with disrupted rest/activity rhythms would not be expected to be inactive or sleep at night as regularly as most people and could have increased exposure to light. Disruption of melatonin secretion rhythms likely alters other biological circadian rhythms, including cortisol. These relationships are worthy of further study. It would be interesting to follow patients longitudinally to determine whether the initial disruption of activity rhythms is related to subsequent

disruption of circadian cortisol rhythms that were not observed in the period immediately after diagnosis. Such a study would extend the findings of the current study and inform a more complete model of relationships between psychosocial variables and circadian disruption.

Contributors

A number of people contributed to this study. Contributors are listed in Table 17 below, with their roles briefly described. Patients were enrolled in this study by Eric Dedert (17), Elizabeth Lush (15), Meagan Martin (11), and Patrick Rhodes (2). Numbers in parentheses indicate the number of patients included in some primary analyse who were enrolled by each researcher.

Table 16. Study personnel and roles on the current project.

Study Personnel:			
Name	**Title**	**Department**	**Role on Project**
Sandra Sephton, Ph.D.	Associate Professor	Psychological & Brain Sciences	Principal Investigator
Anees Chagpar, M.D., M.Sc.	Assistant Professor	Medicine, Surgery	Co-Principal Investigator, Referring Physician
Paul Salmon, Ph.D.	Associate Professor	Psychological & Brain Sciences	Co-Principal Investigator
Jamie Studts, Ph.D.	Associate Professor	Behavioral Science	Co-Principal Investigator
Eric Dedert, M.A.	Graduate Student	Psychological & Brain Sciences	Project Director
Elizabeth Lush	Graduate Student	Psychological & Brain Sciences	Project Director
Kelly McMasters, M.D., Ph.D.	Professor and Chair	Surgery	Referring Physician
Meagan Martin	Graduate Student	Psychological & Brain Sciences	Assistant
Patrick Rhodes	Graduate Student	Psychological & Brain Sciences	Assistant
Robyn McLean, M.S.	Laboratory Technologist	Psychological & Brain Sciences	Saliva Assays

Name	Title	Department	Role on Project
Ehab Dayyat, M.D.	Postdoctoral Fellow	Pediatrics	Actigraphy Consultant
Andrea Floyd, M.A.	Graduate Student	Psychological & Brain Sciences	Assistant
Jesse Thornton	Graduate Student	Spalding University Psychology Department	Assistant
Amanda Mattingly	Honors Student	Psychological & Brain Sciences	Assistant
Jennifer Wrubel	Honors Student	Psychological & Brain Sciences	Assistant
Steven Kniffley	Honors Student	Psychological & Brain Sciences	Assistant

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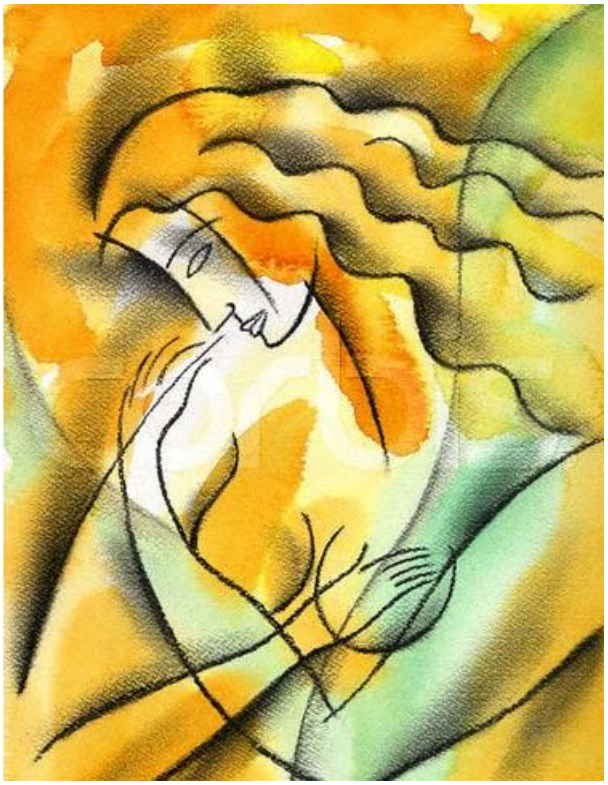
Stress, Coping, and Sleep in Breast Cancer

Home-Based Data Collection: Instructions and Questionnaires



Sandra Sephton, Ph.D., Director
Biobehavioral Research Laboratory
University of Louisville
2301 S. Third Street, 427 Lutz Hall
Louisville, KY 40208

Instructions

Please read this the evening before you begin data collection

Thank you for providing saliva samples and activity data for three full days. We appreciate your careful attention to the details necessary for good data collection in this study! This set of instructions will guide you through each part of the study over the next three days. If you have any questions or difficulties, please call the study Project Director **Elizabeth Lush: (502) 298-4561.**

NOTE: If you have any bleeding in your mouth you should wait until after it heals to complete the study. Even a tiny amount of blood in the saliva will interfere with cortisol measurement.

I. You received a black plastic box to store saliva samples after you complete each collection. Please place the empty box in your refrigerator.

II. Please assemble the following items, and place them at your bedside:

- This instruction packet
- The white "**trackcap**" bottle containing cotton swabs for saliva collection. The purpose of the trackcap is to record the exact time you collect saliva samples. This information is needed to study your cortisol rhythm. Never open the trackcap before you are ready to take a sample!
- The small black case containing "**salivettes**" (tubes for holding saliva samples)
- The black **"Sharpie" pen** provided in the case (for you to write on the tubes).

III. During the next three days you will collect **four** saliva samples at **set times** during the day. You will also complete questionnaires **each morning** just after you provide your first saliva sample in the morning. Open the black case and take out the salivettes labeled "day 1." Note the labels are color coded by collection time as follows:

TIME of SAMPLE	LABEL COLOR
IMMEDIATELY after you wake up in the morning	YELLOW
EXACTLY 30 minutes after you wake up	GREEN
4 PM	GRAY
Just before going to bed	PINK

IV. Prepare to provide saliva samples for early tomorrow morning:

- From the black case, take out two tubes and put them where you can easily reach them from your bed when you first wake up in the morning:

  Day 1: WAKING (yellow)

  Day 1: 30 minutes after awakening (green)

- Set out the white "**trackcap**" bottle containing cotton swabs for saliva collection.
- Take out the marking pen and set it next to the tubes.

V. Please wear the actiwatch all the time during the next three days and nights---except when showering, bathing, swimming, or doing anything else that would immerse the watch in water (it is **NOT** waterproof!). Please note the time you remove the watch and the time you put it back on. The watch will continuously record your level of physical activity, providing data used to measure your sleep-wake rhythms.

If you are not wearing the actiwatch, please put it on your non-dominant wrist now

COLLECTING SALIVA SAMPLES

VI. **How** to collect saliva samples:

- Open the "**trackcap**" bottle. Remove one cotton swab. Close the cap again, tightly.
- Place swab in your mouth and gently move it around with your tongue to soak up saliva. Keep the cotton in your mouth until it feels full like a wet sponge. This usually takes a minute or two, but can take longer. If you have trouble getting enough saliva, try imagining the smell of a lemon.
- While the cotton is in your mouth, use the black **"Sharpie" pen** to write the **date, your ID number** and the **exact time** on the correct salivette tube. Please record the time to the minute (e.g., 5:06). Circle "AM" or "PM" accordingly.
- When the cotton swab feels full of saliva, open the salivette. Spit the cotton swab into the small plastic holder that rests inside the tube, and cap the tube very tightly again.
- Place the salivette in the black plastic box in your refrigerator. Sometimes it may be inconvenient to immediately refrigerate your sample. For example, if you are away from home when you take the 4 pm sample you may refrigerate it later that evening. Samples should not be left out for more than a day.

VII. **When** to collect saliva samples:

Waking sample. For the next three mornings, the moment you wake up in the morning—when you are ready to arise for the day—provide the "WAKING (yellow) sample. After you collect this sample you may get out of bed and continue your usual routine for the next 30 minutes.

NOTE: Please do not eat, drink, brush teeth, use mouthwash, chew gum, or smoke for 30 minutes before providing any saliva sample. These things can interfere with the measurement. Please do not put anything in your mouth until after you have completed the waking sample, the short questionnaire, and the 30 minutes post-waking sample.

30 Minutes after Waking. Exactly 30 minutes after waking—please provide the 30 minute (green) sample each morning.

4 p.m. At 4p.m. each day, please provide the (gray) sample.

Bedtime. Just before going to bed each night, please provide the (pink) sample. You should give your first bedtime sample tomorrow evening.

Are you ready to begin?

- Plan to note the exact times you remove and the activity watch to shower or bathe as well as the exact times you get into bed and begin trying to fall asleep. We'll need to know both the time you take it off and the time you put it back on, to the minute. Please record this information, along with any problems during saliva collection, in the **Saliva and Activity Watch Log** (located at the end of this packet).

- Plan on completing the **Daily Questionnaires** and **Cortisol Questionnaire** just after you provide your first saliva sample in the morning.

If you have any questions please do not hesitate to call us:
Study Telephone Number: 852-5562
Elizabeth Lush Telephone Number:298-4561

If we are not available, please leave a message and we will call you back as soon as possible.
Thank you very much!

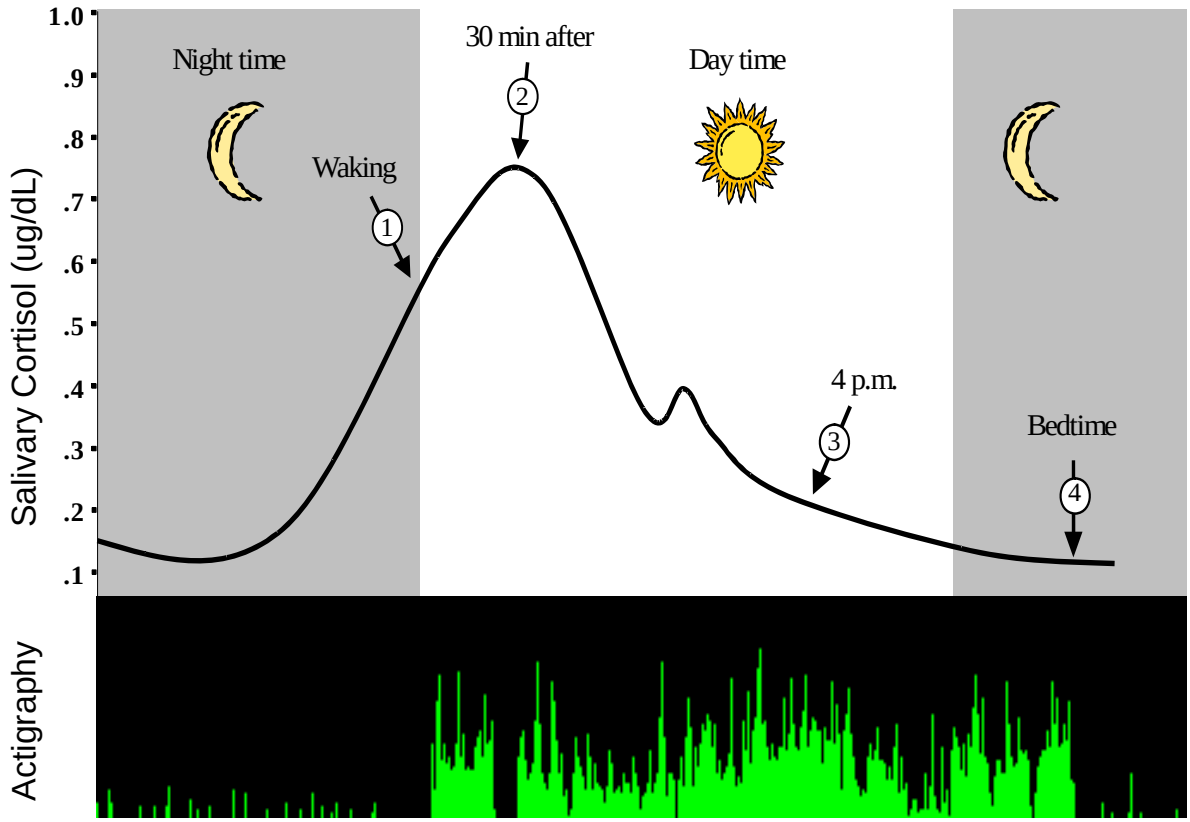
YOUR SALIVA AND ACTIVITY WATCH DATA

SALIVA SAMPLES

Please provide saliva samples when you wake in the morning (#1 in the figure below), 30 minutes after waking (#2), at 4 pm (#3), and at bedtime (#4) on three consecutive days. We will measure the levels of the stress hormone, cortisol, in these samples. The graph below shows the usual daily rhythm of cortisol, which may be disrupted by stress, illness, sleep disruption, diet and exercise.

ACTIVITY WATCH

Please wear the “actigraph” on your wrist during the three day period that you provide saliva samples. This device records physical movement to characterize your sleep-wake rhythm. The black and green graph below shows a "normal" rest-activity pattern over a 24 hour period.


1.0
.9
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.3
.2
.1
Salivary Cortisol (ug/dL)
Night time
Waking
30 min after
Day time
4 p.m.
Bedtime
1
2
3
4
Actigraphy

ID _____ DATE ___/___/___

Daily Data Collection Schedule

DAY ONE

Sample 1: Awakening

___ **Take your waking saliva sample immediately. Refer to Saliva Collection Instructions.**

___ Label the correct tube and place it in the plastic box in your refrigerator.

___ Your Activity Watch should still be on your wrist since it is on for 3 days, 24 hours per day. Only take the Activity Watch off during activities in which it may be immersed in water. Record the time duration in which you take the Activity Watch off on the **Saliva and Activity Watch Log** (one log for all days located at the end of the packet).

___ Fill out the Day One **Daily Questionnaires**.

Sample 2: 30 minutes post-waking

___ Take your 30-minute post-waking saliva sample at EXACTLY 30 minutes after your wake time.

___ **Place the salivette fully labeled in the plastic box in your refrigerator.**

Sample 3: 4:00pm

___ **Take your 4:00pm saliva sample.**

___ **Place the salivette fully labeled in the plastic box in your refrigerator.**

Sample 4: Bedtime

___ **Take your Bedtime saliva sample immediately before you go to sleep.**

___ **Place the salivette fully labeled in the plastic box in your refrigerator.**

___ Plan to note the exact times you get into bed and begin trying to fall asleep.

IMPORTANT:

Don't forget to let us know of any comments about saliva samples, as well as exact times you take off your Activity Watch (temporarily) during the day on the **Saliva and Activity Watch Log** sheet.

ID _____ DATE ___/___/___

Daily Questionnaire for DAY ONE
(to be completed immediately after awakening)

Below is a list of comments made by people after stressful life events. Please fill in each item, indicating how frequently the comments were true for you YESTERDAY regarding your diagnosis and treatment of BREAST CANCER. If they did not occur, please mark the "Not at All" column.

	Not at all	Rarely	Sometimes	Often
	0	1	2	3
I thought about it when I didn't mean to.	O	O	O	O
I had trouble falling asleep or staying asleep, because of pictures of thoughts about it that came into my mind.	O	O	O	O
I had waves of strong feelings about it.	O	O	O	O
I had dreams about it.	O	O	O	O
Pictures about it popped into my mind	O	O	O	O
Other things kept making me think about it.	O	O	O	O
Any reminder brought back feelings about it.	O	O	O	O

We are interested in how people respond when they confront the experience of having breast cancer in their lives. There are lots of ways to try to deal with having breast cancer. This questionnaire asks you to indicate what you did and felt yesterday, when you experienced stressful events related to having breast cancer. Obviously, different events bring out somewhat different responses, but think about what you usually did yesterday when you were under a lot of stress related to having breast cancer.

Then respond to each of the following items by filling in one number for each, using the response choices listed just below. Please try to respond to each item separately in your mind from each other item. Choose your answers thoughtfully, and make your answers as true FOR YOU as you can. Please answer every item. There are no "right" or "wrong" answers, so choose the most accurate answer for YOU-- not what you think "most people" would say or do. Indicate what YOU did yesterday when YOU experienced a stressful event related to having breast cancer.

	I didn't do this at all	I did this a little bit	I did this a medium amount	I did this a lot
	1	2	3	4
I've been turning to work or other activities to take my mind off things.	O	O	O	O
I've been saying to myself "this isn't real".	O	O	O	O
I've been giving up trying to deal with it.	O	O	O	O
I've been refusing to believe that it has happened.	O	O	O	O
I've been giving up the attempt to cope.	O	O	O	O
I've been doing something to think about it less, such as going to movies, watching TV, reading, daydreaming, sleeping, or shopping.	O	O	O	O

ID _____ DATE ___/___/___

ACTIVITY WATCH LOG - DAY ONE

UPON AWAKENING (Please complete as soon as possible after waking)

1. Time you got into bed last night: ___:___ **am/pm (circle one)**
2. Time you began trying to fall asleep: ___:___ **am/pm (circle one)**
3. Time you woke up for the last time this morning: ___:___ **am/pm (circle one)**
4. Time you got out of bed this morning**:** ___:___ **am/pm (circle one)**

For the question below, please fill one bubble on the scale from 0 – 100 that best describes your answer. For example, if you slept just as well as you have usually slept in the past few months, you would fill in the bubble = 50. If worse, you would fill in 60, 70, or 80, etc.

5. How well did you sleep last night?

much better than usual	O 0	O 10	O 20	O 30	O 40	O 50	O 60	O 70	O 80	O 90	O 100

much worse than usual

6. Do you have any other comments regarding last night's sleep?

_____

_____

_____

_____

Remember to take saliva samples 30 minutes after you awoke and at 4pm this afternoon.

Please note any times you remove the activity watch.

The questionnaire continues tomorrow morning.
Have a good day!

Daily Data Collection Schedule
DAY TWO

Sample 1: Awakening

___ Take your waking saliva sample immediately. Refer to Saliva Collection Instructions.
___ Label the correct tube and place in the plastic box in your refrigerator.
___ Your Activity Watch should still be on your wrist since it is on for 3 days 24 hours per day. Only take the Activity Watch off during activities in which it may be immersed in water. Record the time duration in which you take the Activity Watch off on the **Saliva and Activity Watch Log** (one log for all days located at the end of the packet).
___ Fill out the Day Two **Daily Questionnaires** and **Cortisol Questionnaire**.

Sample 2: 30 minutes post-waking

___ Take your 30-minute post-waking saliva sample at EXACTLY 30 minutes after your wake time.
___ Place the salivette fully labeled in the plastic box in your refrigerator.

Sample 3: 4:00pm

___ Take your 4:00pm saliva sample.
___ Place the salivette fully labeled in the plastic box in your refrigerator.

Sample 4: Bedtime

___ Take your Bedtime saliva sample immediately before you go to sleep.
___ Place the salivette fully labeled in the plastic box in your refrigerator.
___ Plan to note the exact times you get into bed and begin trying to fall asleep.

IMPORTANT:

Don't forget to let us know of any comments about saliva samples, as well as exact times you take off your Activity Watch (temporarily) during the day on the **Saliva and Activity Watch Log sheet**.

ID _____ DATE ___/___/___

Daily Questionnaire for DAY TWO
(to be completed immediately after awakening)

Below is a list of comments made by people after stressful life events. Please fill in each item, indicating how frequently the comments were true for you YESTERDAY regarding your diagnosis and treatment of BREAST CANCER. If they did not occur, please mark the "Not at All" column.

	Not at all 0	Rarely 1	Sometimes 2	Often 3
I thought about it when I didn't mean to.	O	O	O	O
I had trouble falling asleep or staying asleep, because of pictures of thoughts about it that came into my mind.	O	O	O	O
I had waves of strong feelings about it.	O	O	O	O
I had dreams about it.	O	O	O	O
Pictures about it popped into my mind	O	O	O	O
Other things kept making me think about it.	O	O	O	O
Any reminder brought back feelings about it.	O	O	O	O

We are interested in how people respond when they confront the experience of having breast cancer in their lives. There are lots of ways to try to deal with having breast cancer. This questionnaire asks you to indicate what you did and felt yesterday, when you experienced stressful events related to having breast cancer. Obviously, different events bring out somewhat different responses, but think about what you did yesterday when you were under a lot of stress related to having breast cancer.

Then respond to each of the following items by filling in one number for each, using the response choices listed just below. Please try to respond to each item separately in your mind from each other item. Choose your answers thoughtfully, and make your answers as true FOR YOU as you can. Please answer every item. There are no "right" or "wrong" answers, so choose the most accurate answer for YOU-- not what you think "most people" would say or do. Indicate what YOU did yesterday when YOU experienced a stressful event related to having breast cancer.

	I didn't do this at all 1	I did this a little bit 2	I did this a medium amount 3	I did this a lot 4
I've been turning to work or other activities to take my mind off things.	O	O	O	O
I've been saying to myself "this isn't real".	O	O	O	O
I've been giving up trying to deal with it.	O	O	O	O
I've been refusing to believe that it has happened.	O	O	O	O
I've been giving up the attempt to cope.	O	O	O	O
I've been doing something to think about it less, such as going to movies, watching TV, reading, daydreaming, sleeping, or shopping.	O	O	O	O

ID _____ DATE ___/___/___

ACTIVITY WATCH LOG - DAY TWO

UPON AWAKENING (Please complete as soon as possible after waking)

1. Time you got into bed last night: ___:___ **am/pm (circle one)**
2. Time you began trying to fall asleep: ___:___ **am/pm (circle one)**
3. Time you woke up for the last time this morning: ___:___ **am/pm (circle one)**
4. Time you got out of bed this morning**:** ___:___ **am/pm (circle one)**

For the question below, please fill one bubble on the scale from 0 – 100 that best describes your answer. For example, if you slept just as well as you have usually slept in the past few months, you would fill in the bubble = 50. If worse, you would fill in 60, 70, or 80, etc.

5. How well did you sleep last night?

much better than usual	O 0	O 10	O 20	O 30	O 40	O 50	O 60	O 70	O 80	O 90	O 100	much worse than usual

6. Do you have any other comments regarding last night's sleep?

_____

_____

_____

Please continue to the next page

ID _____ DATE ___/___/___

Cortisol Questionnaire for <u>DAY TWO</u>
(to be completed immediately after awakening)

Please choose the number that best describes your experience or activities yesterday. Please answer by comparing yesterday with "your average day" over the last few months. Rate your experience yesterday by filling in a bubble from 0 – 100 on the scale below each statement. For example, for question 1 if you were just about as physically active yesterday as you have usually been in the past few months, you would fill in the bubble = 50. If you exercised more than usual, you would fill in 60, 70, or 80, etc.

1. How much physical activity or exercise did you have yesterday?

much less physically active than usual	O **0**	O **10**	O **20**	O **30**	O **40**	O **50**	O **60**	O **70**	O **80**	O **90**	O **100**

2. If you exercised yesterday, please fill in the following:
   a) Exercise activity (e.g., walking, running, etc.) _____
   b) Duration _____ minutes
   c) Level of exertion (darken one): O HIGH O MEDIUM O LOW
   d) Time you began to exercise (hour:minutes) _____:_____

3. How would you rate your health yesterday (how generally **<u>well</u>** you felt).

much better than usual	O **0**	O **10**	O **20**	O **30**	O **40**	O **50**	O **60**	O **70**	O **80**	O **90**	O **100**

4. How stressful was your day yesterday?

much less stressful than usual	O **0**	O **10**	O **20**	O **30**	O **40**	O **50**	O **60**	O **70**	O **80**	O **90**	O **100**

5. If yesterday was MORE stressful than usual, what **<u>events during the day</u>**, and/or what **<u>times of day</u>** were particularly stressful?

Event: _____
Time it began to be stressful: ____:____ (hour:minutes)

Event: _____
Time it began to be stressful: ____:____ (hour:minutes)

6. How much pain did you experience yesterday?

much less pain than usual	O **0**	O **10**	O **20**	O **30**	O **40**	O **50**	O **60**	O **70**	O **80**	O **90**	O **100**

7. How well did you sleep the night before last night?

much better than usual	O **0**	O **10**	O **20**	O **30**	O **40**	O **50**	O **60**	O **70**	O **80**	O **90**	O **100**

8. If you smoke, how many cigarettes (cigars, or pipes) did you smoke yesterday?

PLEASE LEAVE THIS QUESTION BLANK IF YOU DON'T SMOKE

much less than usual	O **0**	O **10**	O **20**	O **30**	O **40**	O **50**	O **60**	O **70**	O **80**	O **90**	O **100**

9. If you drink alcoholic beverages, how many drinks did you have yesterday?

PLEASE LEAVE THIS QUESTION BLANK IF YOU DON'T DRINK ALCOHOL

much less than usual	O **0**	O **10**	O **20**	O **30**	O **40**	O **50**	O **60**	O **70**	O **80**	O **90**	O **100**

10. If you drink caffeinated beverages, how many did you have yesterday?

PLEASE LEAVE THIS QUESTION BLANK IF YOU DON'T USE CAFFEINATED DRINKS

much less than usual	O **0**	O **10**	O **20**	O **30**	O **40**	O **50**	O **60**	O **70**	O **80**	O **90**	O **100**

Remember to take saliva samples 30 minutes after you awoke and at 4pm this afternoon.

Please note any times you remove the activity watch.

The questionnaire continues tomorrow morning.

Have a good day!

Daily Data Collection Schedule

DAY THREE

Sample 1: Awakening

___ Take your waking saliva sample immediately. Refer to Saliva Collection Instructions.

___ Label the correct tube and place it in the plastic box in your refrigerator.

___ Your Activity Watch should still be on your wrist since it is on for 3 days 24 hours per day. Only take the Activity Watch off during activities in which it may be immersed in water. Record the time duration in which you take the Activity Watch off on the **Saliva and Activity Watch Log** (one log for all days at the end of the packet).

___ Fill out the Day Three **Daily Questionnaires**.

Sample 2: 30 minutes post-waking

___ Take your 30-minute post-waking saliva sample at EXACTLY 30 minutes after your wake time.

___ Place the salivette fully labeled in the plastic box in your refrigerator.

Sample 3: 4:00pm

___ Take your 4:00pm saliva sample.

___ Place the salivette fully labeled in the plastic box in your refrigerator.

Sample 4: Bedtime

___ Take your Bedtime saliva sample immediately before you go to sleep.

___ Place the salivette fully labeled in the plastic box in your refrigerator.

___ Plan to note the exact times you get into bed and begin trying to fall asleep.

IMPORTANT:

Don't forget to let us know of any comments about saliva samples, as well as exact times you take off your Activity Watch (temporarily) during the day on the **Saliva and Activity Watch Log sheet**.

ID _____ DATE ___/___/___

Daily Questionnaire for DAY THREE
(to be completed immediately after awakening)

Below is a list of comments made by people after stressful life events. Please fill in each item, indicating how frequently the comments were true for you YESTERDAY regarding your diagnosis and treatment of BREAST CANCER. If they did not occur, please mark the "Not at All" column.

	Not at all	Rarely	Sometimes	Often
	0	1	2	3
I thought about it when I didn't mean to.	O	O	O	O
I had trouble falling asleep or staying asleep, because of pictures of thoughts about it that came into my mind.	O	O	O	O
I had waves of strong feelings about it.	O	O	O	O
I had dreams about it.	O	O	O	O
Pictures about it popped into my mind	O	O	O	O
Other things kept making me think about it.	O	O	O	O
Any reminder brought back feelings about it.	O	O	O	O

We are interested in how people respond when they confront the experience of having breast cancer in their lives. There are lots of ways to try to deal with having breast cancer. This questionnaire asks you to indicate what you did and felt yesterday, when you experienced stressful events related to having breast cancer. Obviously, different events bring out somewhat different responses, but think about what you did yesterday when you were under a lot of stress related to having breast cancer.

Then respond to each of the following items by filling in one number for each, using the response choices listed just below. Please try to respond to each item separately in your mind from each other item. Choose your answers thoughtfully, and make your answers as true FOR YOU as you can. Please answer every item. There are no "right" or "wrong" answers, so choose the most accurate answer for YOU-- not what you think "most people" would say or do. Indicate what YOU did yesterday when YOU experienced a stressful event related to having breast cancer.

	I didn't do this at all	I did this a little bit	I did this a medium amount	I did this a lot
	1	2	3	4
I've been turning to work or other activities to take my mind off things.	O	O	O	O
I've been saying to myself "this isn't real".	O	O	O	O
I've been giving up trying to deal with it.	O	O	O	O
I've been refusing to believe that it has happened.	O	O	O	O
I've been giving up the attempt to cope.	O	O	O	O
I've been doing something to think about it less, such as going to movies, watching TV, reading, daydreaming, sleeping, or shopping.	O	O	O	O

,

ID _____ DATE ___/___/___

ACTIVITY WATCH LOG - DAY THREE

UPON AWAKENING (Please complete as soon as possible after waking)

1. Time you got into bed last night: ___:___ **am/pm (circle one)**
2. Time you began trying to fall asleep: ___:___ **am/pm (circle one)**
3. Time you woke up for the last time this morning: ___:___ **am/pm (circle one)**
4. Time you got out of bed this morning**:** ___:___ **am/pm (circle one)**

For the question below, please fill one bubble on the scale from 0 – 100 that best describes your answer. For example, if you slept just as well as you have usually slept in the past few months, you would fill in the bubble = 50. If worse, you would fill in 60, 70, or 80, etc.

5. How well did you sleep last night?

much better	O	O	O	O	O	O	O	O	O	O	O
than usual	0	10	20	30	40	50	60	70	80	90	100

6. Do you have any other comments regarding last night's sleep?

_____

_____

_____

_____

Please continue to the next page

ID _____ DATE ___/___/___

Cortisol Questionnaire for <u>DAY THREE</u>
(to be completed immediately after awakening)

Please choose the number that best describes your experience or activities yesterday. Please answer by comparing yesterday with "your average day" over the last few months. Rate your experience yesterday by filling in a bubble from 0 – 100 on the scale below each statement. For example, for question 1 if you were just about as physically active yesterday as you have usually been in the past few months, you would fill in the bubble = 50. If you exercised more than usual, you would fill in 60, 70, or 80, etc.

1. How much physical activity or exercise did you have yesterday?

much less physically active than usual	O **0**	O **10**	O **20**	O **30**	O **40**	O **50**	O **60**	O **70**	O **80**	O **90**	O **100**

2. If you exercised yesterday, please fill in the following:
   a) Exercise activity (e.g., walking, running, etc.) _____
   b) Duration _____ minutes
   c) Level of exertion (darken one): O HIGH O MEDIUM O LOW
   d) Time you began to exercise (hour:minutes) _____:_____

3. How would you rate your health yesterday (how generally **<u>well</u>** you felt).

much better than usual	O **0**	O **10**	O **20**	O **30**	O **40**	O **50**	O **60**	O **70**	O **80**	O **90**	O **100**

4. How stressful was your day yesterday?

much less stressful than usual	O **0**	O **10**	O **20**	O **30**	O **40**	O **50**	O **60**	O **70**	O **80**	O **90**	O **100**

5. If yesterday was MORE stressful than usual, what **<u>events during the day</u>**, and/or what **<u>times of day</u>** were particularly stressful?

Event: _____
Time it began to be stressful: ____:____ (hour:minutes)

Event: _____
Time it began to be stressful: ____:____ (hour:minutes)

6. How much pain did you experience yesterday?

much less pain than usual	O **0**	O **10**	O **20**	O **30**	O **40**	O **50**	O **60**	O **70**	O **80**	O **90**	O **100**

7. How well did you sleep the night before last night?

much better than usual	O **0**	O **10**	O **20**	O **30**	O **40**	O **50**	O **60**	O **70**	O **80**	O **90**	O **100**

8. If you smoke, how many cigarettes (cigars, or pipes) did you smoke yesterday?

PLEASE LEAVE THIS QUESTION BLANK IF YOU DON'T SMOKE

much less than usual	O **0**	O **10**	O **20**	O **30**	O **40**	O **50**	O **60**	O **70**	O **80**	O **90**	O **100**

9. If you drink alcoholic beverages, how many drinks did you have yesterday?

PLEASE LEAVE THIS QUESTION BLANK IF YOU DON'T DRINK ALCOHOL

much less than usual	O **0**	O **10**	O **20**	O **30**	O **40**	O **50**	O **60**	O **70**	O **80**	O **90**	O **100**

10. If you drink caffeinated beverages, how many did you have yesterday?

PLEASE LEAVE THIS QUESTION BLANK IF YOU DON'T USE CAFFEINATED DRINKS

much less than usual	O **0**	O **10**	O **20**	O **30**	O **40**	O **50**	O **60**	O **70**	O **80**	O **90**	O **100**

Remember to take saliva samples 30 minutes after you awoke and at 4pm this afternoon.

Please note any times you remove the activity watch.

The questionnaire continues tomorrow morning.

Have a good day!

Daily Data Collection Schedule
DAY FOUR
Awakening

___ Fill out the Day Four **Daily Questionnaires**, **Activity Watch Questionnaire**, and **Cortisol Questionnaire.**

___ **You may take off the Activity watch. Keep them with the supplies (but not in the plastic box with the saliva samples) to return to the research staff.**

ID _____ DATE ___/___/___

Daily Questionnaire for DAY FOUR
(to be completed immediately after awakening)

Below is a list of comments made by people after stressful life events. Please fill in each item, indicating how frequently the comments were true for you YESTERDAY regarding your diagnosis and treatment of BREAST CANCER. If they did not occur, please mark the "Not at ALL" column.

	Not at all	Rarely	Sometimes	Often
	0	1	2	3
I thought about it when I didn't mean to.	O	O	O	O
I had trouble falling asleep or staying asleep, because of pictures of thoughts about it that came into my mind.	O	O	O	O
I had waves of strong feelings about it.	O	O	O	O
I had dreams about it.	O	O	O	O
Pictures about it popped into my mind	O	O	O	O
Other things kept making me think about it.	O	O	O	O
Any reminder brought back feelings about it.	O	O	O	O

We are interested in how people respond when they confront the experience of having breast cancer in their lives. There are lots of ways to try to deal with having breast cancer. This questionnaire asks you to indicate what you did and felt yesterday, when you experienced stressful events related to having breast cancer. Obviously, different events bring out somewhat different responses, but think about what you did yesterday when you were under a lot of stress related to having breast cancer.

Then respond to each of the following items by filling in one number for each, using the response choices listed just below. Please try to respond to each item separately in your mind from each other item. Choose your answers thoughtfully, and make your answers as true FOR YOU as you can. Please answer every item. There are no "right" or "wrong" answers, so choose the most accurate answer for YOU-- not what you think "most people" would say or do. Indicate what YOU did yesterday when YOU experienced a stressful event related to having breast cancer.

	I didn't do this at all	I did this a little bit	I did this a medium amount	I did this a lot
	1	2	3	4
I've been turning to work or other activities to take my mind off things.	O	O	O	O
I've been saying to myself "this isn't real".	O	O	O	O
I've been giving up trying to deal with it.	O	O	O	O
I've been refusing to believe that it has happened.	O	O	O	O
I've been giving up the attempt to cope.	O	O	O	O
I've been doing something to think about it less, such as going to movies, watching TV, reading, daydreaming, sleeping, or shopping.	O	O	O	O

ID _____ DATE ___/___/___

ACTIVITY WATCH LOG - DAY FOUR
UPON AWAKENING

1. Time you got into bed last night: ___:___ **am/pm (circle one)**
2. Time you began trying to fall asleep: ___:___ **am/pm (circle one)**
3. Time you woke up for the last time this morning: ___:___ **am/pm (circle one)**
4. Time you got out of bed this morning**:** ___:___ **am/pm (circle one)**

For the question below, please fill one bubble on the scale from 0 – 100 that best describes your answer. For example, if you slept just as well as you have usually slept in the past few months, you would fill in the bubble = 50. If worse, you would fill in 60, 70, or 80, etc.

5. How well did you sleep last night?

much better	O	O	O	O	O	O	O	O	O	O	O
than usual	0	10	20	30	40	50	60	70	80	90	100

6. Do you have any other comments regarding last night's sleep?

_____

_____

_____

_____

Please continue to the next page

ID _____ DATE ___/___/___

Cortisol Questionnaire for <u>DAY FOUR</u>
(to be completed immediately after awakening)

Please choose the number that best describes your experience or activities yesterday. Please answer by comparing yesterday with "your average day" over the last few months. Rate your experience yesterday by filling in a bubble from 0 – 100 on the scale below each statement. For example, for question 1 if you were just about as physically active yesterday as you have usually been in the past few months, you would fill in the bubble = 50. If you exercised more than usual, you would fill in 60, 70, or 80, etc.

1. How much physical activity or exercise did you have yesterday?

much less physically active than usual	O **0**	O **10**	O **20**	O **30**	O **40**	O **50**	O **60**	O **70**	O **80**	O **90**	O **100**

2. If you exercised yesterday, please fill in the following:
   a) Exercise activity (e.g., walking, running, etc.) _____
   b) Duration _____ minutes
   c) Level of exertion (darken one): O HIGH O MEDIUM O LOW
   d) Time you began to exercise (hour:minutes) _____:_____

3. How would you rate your health yesterday (how generally **<u>well</u>** you felt).

much better than usual	O **0**	O **10**	O **20**	O **30**	O **40**	O **50**	O **60**	O **70**	O **80**	O **90**	O **100**

4. How stressful was your day yesterday?

much less stressful than usual	O **0**	O **10**	O **20**	O **30**	O **40**	O **50**	O **60**	O **70**	O **80**	O **90**	O **100**

5. If yesterday was MORE stressful than usual, what **<u>events during the day</u>**, and/or what **<u>times of day</u>** were particularly stressful?

Event: _____
Time it began to be stressful: ____:____ (hour:minutes)

Event: _____
Time it began to be stressful: ____:____ (hour:minutes)

6. How much pain did you experience yesterday?

much less pain than usual	O **0**	O **10**	O **20**	O **30**	O **40**	O **50**	O **60**	O **70**	O **80**	O **90**	O **100**

7. How well did you sleep the night before last night?

much better than usual	O **0**	O **10**	O **20**	O **30**	O **40**	O **50**	O **60**	O **70**	O **80**	O **90**	O **100**

8. If you smoke, how many cigarettes (cigars, or pipes) did you smoke yesterday?

PLEASE LEAVE THIS QUESTION BLANK IF YOU DON'T SMOKE

much less than usual	O **0**	O **10**	O **20**	O **30**	O **40**	O **50**	O **60**	O **70**	O **80**	O **90**	O **100**

9. If you drink alcoholic beverages, how many drinks did you have yesterday?

PLEASE LEAVE THIS QUESTION BLANK IF YOU DON'T DRINK ALCOHOL

much less than usual	O **0**	O **10**	O **20**	O **30**	O **40**	O **50**	O **60**	O **70**	O **80**	O **90**	O **100**

10. If you drink caffeinated beverages, how many did you have yesterday?

PLEASE LEAVE THIS QUESTION BLANK IF YOU DON'T USE CAFFEINATED DRINKS

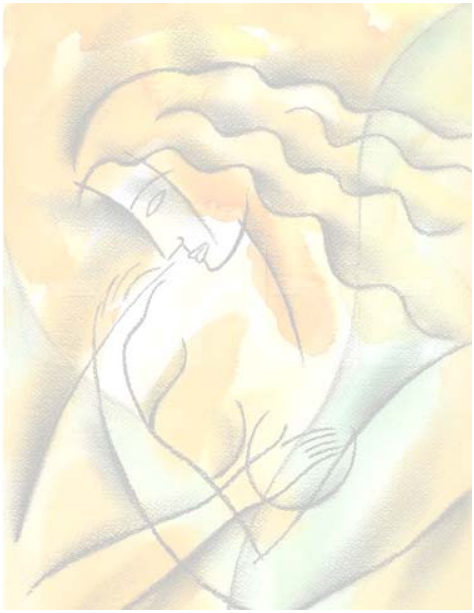
much less than usual	O **0**	O **10**	O **20**	O **30**	O **40**	O **50**	O **60**	O **70**	O **80**	O **90**	O **100**

Saliva and Activity Watch Log Sheet

	Saliva Please write about any problems with saliva collection		**Watch** Please write down any times the Actiwatch is removed	
	Date/Time	**Comments**	**Date/Time**	**Comments**
Example	*1/1/06 4:12 p.m.*	*Late taking 4 p.m. sample*	*1/1/06 6:37 - 7:12 p.m.*	*Washed dishes*
DAY 0				
DAY 1				
DAY 2				

Saliva and Activity Watch Log Sheet

	Saliva		Watch	
	Please write about any problems with saliva collection		Please write down any times the Actiwatch is removed	
	Date/Time	**Comments**	**Date/Time**	**Comments**
Example	*1/1/06 4:12 p.m.*	*Late taking 4 p.m. sample*	*1/1/06 6:37 - 7:12 p.m.*	*Washed dishes*
DAY 3				
DAY 4				

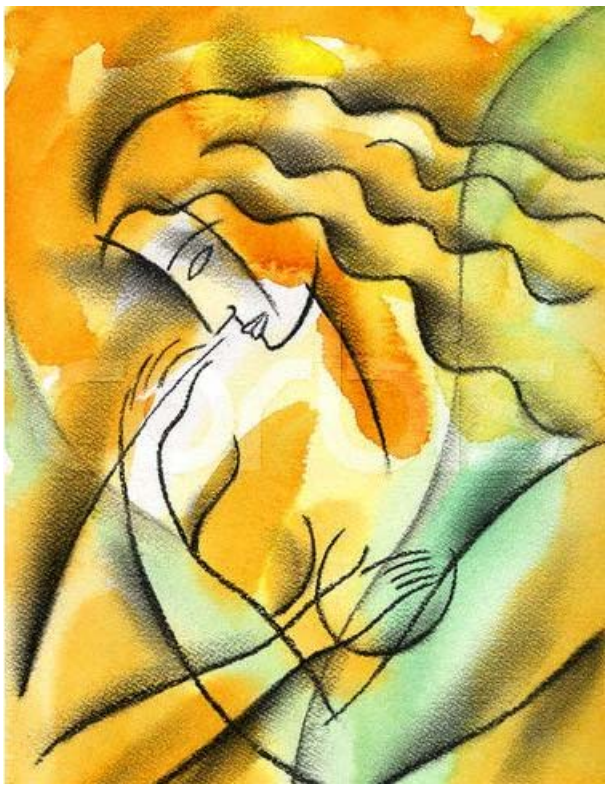


You Are Finished!

Thank You So Much For Your Time and Patience!

Stress, Coping, and Sleep in Breast Cancer

Questionnaire Packet



Sandra Sephton, Ph.D., Director
Biobehavioral Research Laboratory
University of Louisville
2301 S. Third Street, 427 Lutz Hall
Louisville, KY 40208

Stress, Coping, and Sleep in Breast Cancer

Questionnaire Packet

Instructions:

Dear Research Participant.

We greatly appreciate your willingness to take part in this study of the effects of stress, coping, and sleep in women with breast cancer. It may take you about one hour to complete this packet. Please complete it in a quiet place, alone, at a time when you can be free from interruption.

- **Please be sure to write the date that you answer <u>each</u> questionnaire at the top of the page on which it begins.**
- **Please <u>fill in the bubbles</u> so that the entire circle is blackened (do NOT make check marks)**
- **Do not skip any items**
- **Please use a dark pen and write clearly DO <u>NOT</u> USE PENCIL**
- **If you make any mistakes, please put an "X" through the incorrect answer and fill in the correct answer.**

By completing this questionnaire, you will help us understand much about stress in cancer. We hope this will be a valuable experience for you as well as for us. We are very grateful to you for making the commitment to participate. Your role in this research is vital. You may feel as though you are answering the same question more than once; however, your answer on each item is needed.

The timing of your menstrual cycle, your physical condition, and some of the medications you may be taking are likely to influence the stress hormones we will be measuring in your blood, urine and saliva samples. Thus, please be as accurate as possible when recording your medical information. To maintain the confidentiality of the information you provide, all data will be secured in locked files and will be accessed only by research staff. In some of the enclosed questionnaires you will be asked to answer questions about past stressful experiences. This may bring up painful feelings or memories. If you experience so much distress that you would benefit from personal counseling, the investigators can refer you to the Behavioral Medicine Clinic at Norton Hospital, although the study cannot provide payment for such treatment. If you have concerns or questions that come up in the process of completing these questionnaires, you may contact Sandra Sephton.

With our sincere thanks,

Sandra Sephton, Ph.D. (502-852-1166)

Thank you very much for participating in this study!

BAK

Please answer the following questions about your background and medical history.

1. Name:_____

2. Nickname:_____

3. Age:_____

4. Gender: Male O Female O

5. Date of Birth: Month: _____ Day: _____ Year: _____

6. Address:

   Street _____ Apt. # _____

   City _____ State_____ Zip _____

   Phone Number:_____

7. Family/Friend Caregiver Support? O Yes O No

   Name _____

   Phone Number _____

. Diagnosing physician:

   Name:_____ Phone number:_____

   Location (practice, clinic or hospital, city):_____

9. Date of first breast cancer diagnosis (mm/dd/yy):

_____

10. On which side was your cancer? _____

11. Stage at diagnosis: : _____

12. Have you EVER had radiation therapy? O Yes O No

13. Are you currently receiving radiation therapy? O Yes O No

    DATE STARTED? Month_____ Year_____ DATE ENDED?_____

BAK

14. When was the **last date** of your radiation therapy? (mm/dd/yy):
_____

15. Have you EVER had chemotherapy treatment? O Yes O No

DATE STARTED? (mm/dd/yy): _____

16. Are you currently receiving chemotherapy treatment? O Yes O No

DATE STARTED? (mm/dd/yy): _____

17. When was the **last date** of your chemotherapy treatment? (mm/dd/yy):
_____

18. Have you had a breast or part of a breast removed surgically? (mm/dd/yy):
_____

Which breast or part of your breast?_____

19. Have you been diagnosed with any other type of cancer?:

When? (mm/dd/yy):
_____

What kind of cancer?_____

Treatment?_____

20. Have you been diagnosed with other ongoing medical conditions (diabetes, cardiovascular disease, high blood pressure, renal disease, etc.)?

_____
_____

21. Do you have children? O Yes O No
If so, how many children have you had?
Number of children you have had: _____
Number of children living with you: _____
Number of elderly parents living with you: _____
Number of other people living with you: _____

BAK

22. What is your marital status?

- O Single, never married
- O Single, divorced
- O Single, living with partner
- O Married
- O Divorced and remarried
- O Widowed
- O Widowed and remarried
- O Separated
- O Other

23. If you are separated, divorced, or widowed, when did this occur? Month _____ Year _____

24. What is your racial-ethnic background?

- O Asian
- O Black
- O Hispanic
- O Native American
- O White/Caucasian
- O Other

25. How many years of education have you completed?
Use the following numbers as a guide to your answer:

- O Grade School = K-6
- O Middle School = 7-8
- O High School = 12
- O AA/Technical = 14
- O BA/BS = 16
- O MA = 18
- O PhD, MD, JD = 20

26. Are you currently employed? O Yes O No

27. If currently employed: Hours per week? (enter 0 if not applicable) : _____

Occupation: _____

28. If not currently employed, which of the following best describes your situation?

- O Not looking for work
- O Looking for work
- O Leave of Absence
- O Retired
- O Medical leave or temporary disability
- O Permanently disabled
- O Not applicable

BAK

29. If not currently employed, what was your previous occupation, if any?

_____

30. What is your total annual household income before taxes?

- O Less than $20,000
- O $20,000 - $39,999
- O $40,000 - $59,999
- O $60,000 - $79,999
- O $80,000 - $99,999
- O $100,000 and above

31. What is your current living situation?
(Do not include temporary visitors.)

- O Live alone
- O Live with spouse/partner only
- O Live with spouse/partner and child only
- O Live with child or children only
- O Live with other relatives
- O Live with other non-relatives
- O Other

32. Do you own or rent your place of residence? O Own O Rent

33. What is the total number of people living in your household, including yourself?

_____

34. What is your religious affiliation? (darken one)

- O Protestant
- O Jewish
- O Catholic
- O None
- O Other_____(please specify)

35. Insurance:

Private	O
Public	O
Other	O
None	O

36. Do you consider yourself to be?

- O pre-menopause (you have a menstrual period on a regular cycle)
- O peri-menopause (you have begun to experience symptoms of menopause, but have not completed this transition)
- O post-menopause (you no longer menstruate, and have completed the transition into menopause)

BAK

37. If you currently experience a regular menstrual period, what was the first day of your last menstrual period?
(mm/dd/yy): _____

38. If you currently experience a regular menstrual period, how many days is your usual cycle (days from the beginning of one period to the beginning of the next one, for example, 28 days, 31 days, etc.).

_____ # days

39. Do you currently use oral contraceptive pills? O Yes O No

40. Are you currently taking estrogen replacement therapy? O Yes O No

MEDS

Please list all medications you have taken in the past month. Please include prescription medications and non-prescription (over-the-counter) medications, as well as any herbal supplements. You may find it helpful to have your medications at hand while completing this form. *Please use the back of this page if you need additional room.*

Medication	Dosage	Number of times per day	Number of days per week	Reason taken

KAR

100	Normal, no complaints, no evidence of disease
90	Able to carry on normal activity: minor symptom of disease
80	Normal activity with effort: some symptoms of disease
70	Cares for self: unable to carry on normal activity or active work
60	Requires occasional assistance but is able to care for needs
50	Requires considerable assistance and frequent medical care
40	Disabled: requires special care and assistance
30	Severely disabled: hospitalization is indicated, death not imminent
20	Very sick, hospitalization necessary; active treatment necessary
10	Moribund, fatal processes progressing rapidly
0	Death

IES

Below is a list of comments made by people after stressful life events. Please fill in each item, indicating how frequently the comments were true for you DURING THE CURRENT DAY regarding your diagnosis and treatment of BREAST CANCER. If they did not occur, please mark the "Not at All" column.

	Not at all	Rarely	Sometimes	Never
	0	1	2	3
1. I thought about it when I didn't mean to.	O	O	O	O
2. I avoided letting myself get upset when I thought about it or was reminded of it.	O	O	O	O
3. I tried to remove it from memory.	O	O	O	O
4. I had trouble falling asleep or staying asleep, because of pictures of thoughts about it that came into my mind.	O	O	O	O
5. I had waves of strong feelings about it.	O	O	O	O
6. I had dreams about it.	O	O	O	O
7. I stayed away from reminders of it.	O	O	O	O
8. I felt as if it hadn't happened or it wasn't real.	O	O	O	O
9. I tried not to talk about it.	O	O	O	O
10. Pictures about it popped into my mind.	O	O	O	O
11. Other things kept making me think about it.	O	O	O	O
12. I was aware that I still had a lot of feelings about it, but I didn't deal with them.	O	O	O	O
13. I tried not to think about it.	O	O	O	O
14. Any reminder brought back feelings about it.	O	O	O	O
15. My feelings about it were kind of numb.	O	O	O	O

We are interested in how people respond when they confront difficult or stressful events in their lives that are related to the experience of having breast cancer. There are lots of ways to try to deal with this stress. This questionnaire asks you to indicate what you generally do and feel, when you experience stressful events related to breast cancer. Obviously, different events bring out somewhat different responses, but think about what you usually do when you are under a lot of stress related to breast cancer.

Then respond to each of the following items by filling in one number for each, using the response choices listed just below. Please try to respond to each item separately in your mind from each other item. Choose your answers thoughtfully, and make your answers as true FOR YOU as you can. Please answer every item. There are no "right" or "wrong" answers, so choose the most accurate answer for YOU-- not what you think "most people" would say or do. Indicate what YOU usually do when YOU experience a stressful event related to breast cancer.

	I usually don't do this at all	I usually do this a little bit	I usually do this a medium amount	I usually do this a lot
1. I've been concentrating my efforts on doing something about the situation I'm in.	O	O	O	O
2. I've been trying to come up with a strategy about what to do.	O	O	O	O

	I usually don't do this at all	I usually do this a little bit	I usually do this a medium amount	I usually do this a lot
3. I've been trying to see it in a different light, to make it seem more positive.	O	O	O	O
4. I've been accepting the reality of the fact that it has happened.	O	O	O	O
5. I've been making jokes about it.	O	O	O	O
6. I've been trying to find comfort in my religion or spiritual beliefs.	O	O	O	O
7. I've been getting emotional support from others.	O	O	O	O
8. I've been trying to get advice or help from other people about what to do.	O	O	O	O
9. I've been turning to work or other activities to take my mind off things.	O	O	O	O
10. I've been saying to myself "this isn't real."	O	O	O	O
11. I've been saying things to let my unpleasant feelings escape.	O	O	O	O
12. I've been using alcohol or other drugs to make myself feel better.	O	O	O	O
13. I've been giving up trying to deal with it.	O	O	O	O
14. I've been criticizing myself.	O	O	O	O
15. I've been learning to live with it.	O	O	O	O
16. I've been taking action to try to make the situation better.	O	O	O	O
17. I've been thinking hard about what steps to take.	O	O	O	O
18. I've been looking for something good in what is happening.	O	O	O	O
19. I've been making fun of the situation.	O	O	O	O
20. I've been praying or meditating.	O	O	O	O
21. I've been getting comfort and understanding from someone.	O	O	O	O
22. I've been getting help and advice from other people.	O	O	O	O
23. I've been doing something to think about it less, such as going to movies, watching TV, reading, daydreaming, sleeping, or shopping.	O	O	O	O
24. I've been refusing to believe that it has happened.	O	O	O	O
25. I've been expressing my negative feelings.	O	O	O	O
26. I've been using alcohol or other drugs to help me get through it.	O	O	O	O
27. I've been giving up the attempt to cope.	O	O	O	O
28. I've been blaming myself for things that happened.	O	O	O	O

QOL

Below is a list of statements that other people with your illness have said are important. By circling one number per line, please indicate how true each statement has been for you **during the past 7 days.**

PHYSICAL WELL-BEING	Not at all	A little bit	Somewhat	Quite a bit	Very much
	0	1	2	3	4
1. I have a lack of energy.	O	O	O	O	O
2. I have nausea.	O	O	O	O	O
3. Because of my physical condition, I have trouble meeting the needs of my family.	O	O	O	O	O
4. I have pain.	O	O	O	O	O
5. I am bothered by side effects of treatment.	O	O	O	O	O
6. I feel ill.	O	O	O	O	O
7. I am forced to spend time in bed.	O	O	O	O	O

	Not at all										**Very much so**
8. Looking at the above 7 questions, how much would you say your **PHYSICAL WELL-BEING** affects your quality of life?	0	1	2	3	4	5	6	7	8	9	10
	O	O	O	O	O	O	O	O	O	O	O

SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Somewhat	Quite a bit	Very much
	0	1	2	3	4
9. I feel distant from my friends.	O	O	O	O	O
10. I get emotional support from my family.	O	O	O	O	O
11. I get support from my friends and neighbors.	O	O	O	O	O
12. My family has accepted my illness.	O	O	O	O	O
13. Family communication about my illness is poor.	O	O	O	O	O
14. I feel close to my partner (or the person who is my main support).	O	O	O	O	O

Regardless of your current level of sexual activity, please answer the following questions:

	No	**Yes**
15a. Have you been sexually active during the past year?	O	O

	Not at all	A little bit	Somewhat	Quite a bit	Very much
	0	1	2	3	4
15b. If yes: I am satisfied with my sex life.	O	O	O	O	O

Not at all

Very much so

	0	1	2	3	4	5	6	7	8	9	10
16. Looking at the above 7 questions, how much would you say your **SOCIAL/FAMILY WELL-BEING** affects your quality of life? **QOL**	O	O	O	O	O	O	O	O	O	O	O

RELATIONSHIP WITH DOCTOR

	Not at all	A little bit	Somewhat	Quite a bit	Very much
	0	1	2	3	4
17. I have confidence in my doctor(s).	O	O	O	O	O
18. My doctor is available to answer my questions.	O	O	O	O	O

Not at all

Very much so

	0	1	2	3	4	5	6	7	8	9	10
19. Looking at the above 7 questions, how much would you say your **RELATIONSHIP WITH THE DOCTOR** affects your quality of life?	O	O	O	O	O	O	O	O	O	O	O

EMOTIONAL WELL-BEING

	Not at all	A little bit	Somewhat	Quite a bit	Very much
	0	1	2	3	4
20. I feel sad.	O	O	O	O	O
21. I am proud of how I'm coping with my illness.	O	O	O	O	O
22. I am losing hope in the fight against my illness.	O	O	O	O	O
23. I feel nervous.	O	O	O	O	O
24. I worry about dying.	O	O	O	O	O
25. I worry that my condition will get worse.	O	O	O	O	O

Not at all

Very much so

	0	1	2	3	4	5	6	7	8	9	10
26. Looking at the above 6 questions, how much would you say your **EMOTIONAL WELL-BEING** affects your quality of life?	O	O	O	O	O	O	O	O	O	O	O

FUNCTIONAL WELL-BEING	Not at all	A little bit	Somewhat	Quite a bit	Very much
	0	1	2	3	4
27. I am able to work (include work in home).	O	O	O	O	O
28. My work (include work in home) is fulfilling.	O	O	O	O	O
29. I am able to enjoy life.	O	O	O	O	O
30. I have accepted my illness.	O	O	O	O	O
31. I am sleeping well.	O	O	O	O	O
32. I am enjoying the things I usually do for fun.	O	O	O	O	O
33. I am content with the quality of my life right now.	O	O	O	O	O

	Not at all										**Very much so**
34. Looking at the above 7 questions, how much would you say your **FUNCTIONAL WELL-BEING** affects your quality of life? **QOL**	0	1	2	3	4	5	6	7	8	9	10
	O	O	O	O	O	O	O	O	O	O	O

ADDITIONAL CONCERNS	Not at all	A little bit	Somewhat	Quite a bit	Very much
	0	1	2	3	4
35. I have been short of breath.	O	O	O	O	O
36. I am self-conscious about the way I dress.	O	O	O	O	O
37. One or both of my arms are swollen or tender.	O	O	O	O	O
38. I feel sexually attractive.	O	O	O	O	O
39. I am bothered by hair loss.	O	O	O	O	O
40. I worry about the risk of cancer in other family members.	O	O	O	O	O
41. I worry about the effect of stress on my illness.	O	O	O	O	O
42. I am bothered by a change in weight.	O	O	O	O	O
43. I am able to feel like a woman.	O	O	O	O	O

	Not at all										**Very much so**
44. Looking at the above 9 questions, how much would you say these **ADDITIONAL CONCERNS** affect your quality of life?	0	1	2	3	4	5	6	7	8	9	10
	O	O	O	O	O	O	O	O	O	O	O

ISEL

This scale is made up of a list of statements each of which may or may not be true about you. Choose "definitely true" if you are sure it is true about you and "probably true" if you think it is true but are not absolutely certain. Similarly, you should choose "definitely false" if you are sure the statement is false and "probably false" if you think it is false but are not absolutely certain.

	Definitely False	Probably False	Probably True	Definitely True
	0	1	2	3
1. There are several people that I trust to help solve my problems.	O	O	O	O
2. If I needed help fixing an appliance or repairing my car, there is someone who would help me.	O	O	O	O
3. Most of my friends are more interesting than I am.	O	O	O	O
4. There is someone who takes pride in my accomplishments.	O	O	O	O
5. When I feel lonely, there are several people I can talk to.	O	O	O	O
6. There is no one that I feel comfortable to talking about intimate personal problems.	O	O	O	O
7. I often meet or talk with family or friends.	O	O	O	O
8. Most people I know think highly of me.	O	O	O	O
9. If I needed a ride to the airport very early in the morning, I would have a hard time finding someone to take me.	O	O	O	O
10. I feel like I'm not always included by my circle of friends.	O	O	O	O
11. There really is no one who can give me an objective view of how I'm handling my problems.	O	O	O	O
12. There are several different people I enjoy spending time with.	O	O	O	O
13. I think that my friends feel that I'm not very good at helping them solve their problems.	O	O	O	O

ISEL

	Definitely False	Probably False	Probably True	Definitely True
	0	1	2	3
14. If I were sick and needed someone (friend, family member, or acquaintance) to take me to the doctor, I would have trouble finding someone.	O	O	O	O
15. If I wanted to go on a trip for a day (e.g., to the mountains, beach, or country), I would have a hard time finding someone to go with me.	O	O	O	O
16. If I needed a place to stay for a week because of an emergency (for example, water or electricity out in my apartment or house), I could easily find someone who would put me up.	O	O	O	O
17. I feel that there is no one I can share my most private worries and fears with.	O	O	O	O
18. If I were sick, I could easily find someone to help me with my daily chores.	O	O	O	O
19. There is someone I can turn to for advice about handling problems with my family.	O	O	O	O
20. I am as good at doing things as most other people are.	O	O	O	O
21. If I decide one afternoon that I would like to go to a movie that evening, I could easily find someone to go with me.	O	O	O	O
22. When I need suggestions on how to deal with a personal problem, I know someone I can turn to.	O	O	O	O
23. If I needed an emergency loan of $100, there is someone (friend, relative, or acquaintance) I could get it from.	O	O	O	O
24. In general, people do not have much confidence in me.	O	O	O	O
25. Most people I know do not enjoy the same things that I do.	O	O	O	O
26. There is someone I could turn to for advice about making career plans or changing my job.	O	O	O	O
27. I don't often get invited to do things with others.	O	O	O	O
28. Most of my friends are more successful at making changes in their lives than I am.	O	O	O	O
29. If I had to go out of town for a few weeks, it would be difficult to find someone who would look after my house or apartment (the plants, pets, garden, etc.).	O	O	O	O
30. There really is no one I can trust to give me good financial advice.	O	O	O	O
31. If I wanted to have lunch with someone, I could easily find someone to join me.	O	O	O	O
32. I am more satisfied with my life than most people are with theirs.	O	O	O	O
33. If I was stranded 10 miles from home, there is someone I could call who would come and get me.	O	O	O	O
34. No one I know would throw a birthday party for me.	O	O	O	O
35. It would me difficult to find someone who would lend me their car for a few hours.	O	O	O	O
36. If a family crisis arose, it would be difficult to find someone who could give me good advice about how to handle it.	O	O	O	O
37. I am closer to my friends than most other people are to theirs.	O	O	O	O

ISEL

	Definitely False	Probably False	Probably True	Definitely True
	0	1	2	3
38. There is at least one person I know whose advice I really trust.	O	O	O	O
39. . If I needed some help in moving to a new house or apartment, I would have a hard time finding someone to help me.	O	O	O	O
40. I have a hard time keeping pace with my friends.	O	O	O	O

POM

Below is a list of words that describe feelings people have. Please read each one carefully. Then circle ONE number under the answer to the right which best describes HOW YOU HAVE BEEN FEELING DURING THE PAST WEEK INCLUDING TODAY. The numbers refer to these phrases:

	Not at all	A little	Moderately	Quite a bit	Extremely
	0	1	2	3	4
1. Friendly	O	O	O	O	O
2. Tense	O	O	O	O	O
3. Angry	O	O	O	O	O
4. Worn out	O	O	O	O	O
5. Unhappy	O	O	O	O	O
6. Clear-headed	O	O	O	O	O
7. Lively	O	O	O	O	O
8. Confused	O	O	O	O	O
9. Sorry for things done	O	O	O	O	O
10. Shaky	O	O	O	O	O
11. Listless	O	O	O	O	O
12. Peeved	O	O	O	O	O
13. Considerate	O	O	O	O	O
14. Sad	O	O	O	O	O
15. Active	O	O	O	O	O
16. On edge	O	O	O	O	O
17. Grouchy	O	O	O	O	O
18. Blue	O	O	O	O	O
19. Energetic	O	O	O	O	O
20. Panicky	O	O	O	O	O
21. Hopeless	O	O	O	O	O
22. Relaxed	O	O	O	O	O
23. Unworthy	O	O	O	O	O
24. Spiteful	O	O	O	O	O
25. Sympathetic	O	O	O	O	O

POM

	Not at all	A little	Moderately	Quite a bit	Extremely
	0	**1**	**2**	**3**	**4**
26. Uneasy	O	O	O	O	O
27. Restless	O	O	O	O	O
28. Unable to concentrate	O	O	O	O	O
29. Fatigued	O	O	O	O	O
30. Helpful	O	O	O	O	O
31. Annoyed	O	O	O	O	O
32. Discouraged	O	O	O	O	O
33. Resentful	O	O	O	O	O
34. Nervous	O	O	O	O	O
35. Lonely	O	O	O	O	O
36. Miserable	O	O	O	O	O
37. Muddled	O	O	O	O	O
38. Cheerful	O	O	O	O	O
39. Bitter	O	O	O	O	O
40. Excited	O	O	O	O	O
41. Anxious	O	O	O	O	O
42. Ready to fight	O	O	O	O	O
43. Good-natured	O	O	O	O	O
44. Gloomy	O	O	O	O	O
45. Desperate	O	O	O	O	O
46. Sluggish	O	O	O	O	O
47. Rebellious	O	O	O	O	O
48. Helpless	O	O	O	O	O
49. Weary	O	O	O	O	O
50. Bewildered	O	O	O	O	O
51. Alert	O	O	O	O	O
52. Deceived	O	O	O	O	O
53. Furious	O	O	O	O	O
54. Efficient	O	O	O	O	O
55. Trusting	O	O	O	O	O
56. Full of pep	O	O	O	O	O
57. Bad-tempered	O	O	O	O	O
58. Worthless	O	O	O	O	O
59. Forgetful	O	O	O	O	O
60. Carefree	O	O	O	O	O
61. Terrified	O	O	O	O	O
62. Guilty	O	O	O	O	O
63. Vigorous	O	O	O	O	O
64. Uncertain about things	O	O	O	O	O
65. Bushed	O	O	O	O	O

PFS

For each of the following questions, circle the number that best describes the fatigue you are experiencing now. Please make every effort to answer each question to the best of your ability. Thank you very much.

1. How long have you been feeling fatigued? (*fill one circle only*)
   - O Minutes
   - O Hours
   - O Days
   - O Weeks
   - O Months
   - O Other (please describe): _____

2. To what degree is the fatigue you are feeling now causing you distress?	None	0 O	1 O	2 O	3 O	4 O	5 O	6 O	7 O	8 O	9 O	10 O	A great deal
3. To what degree is the fatigue you are feeling now interfering with your ability to complete your work or school activities?	None	0 O	1 O	2 O	3 O	4 O	5 O	6 O	7 O	8 O	9 O	10 O	A great deal
4. To what degree is the fatigue you are feeling now interfering with your ability to visit or socialize with your friends?	None	0 O	1 O	2 O	3 O	4 O	5 O	6 O	7 O	8 O	9 O	10 O	A great deal
5. To what degree is the fatigue you are feeling now interfering with your ability to engage in sexual activity?	None	0 O	1 O	2 O	3 O	4 O	5 O	6 O	7 O	8 O	9 O	10 O	A great deal
6. Overall how much is the fatigue, which you are experiencing now, interfering with your ability to engage in the kind of activities you enjoy doing?	None	0 O	1 O	2 O	3 O	4 O	5 O	6 O	7 O	8 O	9 O	10 O	A great deal
7. How would you describe the degree of intensity or severity of the fatigue which you are experiencing now?	Mild	0 O	1 O	2 O	3 O	4 O	5 O	6 O	7 O	8 O	9 O	10 O	Severe
8. To what degree would you describe the fatigue which you are experiencing now as being:	Pleasant	0 O	1 O	2 O	3 O	4 O	5 O	6 O	7 O	8 O	9 O	10 O	Unpleasant
9. To what degree would you describe the fatigue which you are experiencing now as being:	Agreeae	0 O	1 O	2 O	3 O	4 O	5 O	6 O	7 O	8 O	9 O	10 O	Disagree-able
10. To what degree would you describe the fatigue which you are experiencing now as being:	Protective	0 O	1 O	2 O	3 O	4 O	5 O	6 O	7 O	8 O	9 O	10 O	Destructive
11. To what degree would you describe the fatigue which you are experiencing now as being:	Positive	0 O	1 O	2 O	3 O	4 O	5 O	6 O	7 O	8 O	9 O	10 O	Negative
12. To what degree would you describe the fatigue which you are experiencing now as being:	Normal	0 O	1 O	2 O	3 O	4 O	5 O	6 O	7 O	8 O	9 O	10 O	Abnormal
13. To what degree are you now feeling:	Strong	0 O	1 O	2 O	3 O	4 O	5 O	6 O	7 O	8 O	9 O	10 O	Weak

14. To what degree are you now feeling:	Awake	0 O	1 O	2 O	3 O	4 O	5 O	6 O	7 O	8 O	9 O	10 O	Sleepy
15. To what degree are you now feeling:	Lively	0 O	1 O	2 O	3 O	4 O	5 O	6 O	7 O	8 O	9 O	10 O	Listless
16. To what degree are you now feeling:	Refreshed	0 O	1 O	2 O	3 O	4 O	5 O	6 O	7 O	8 O	9 O	10 O	Tired
17. To what degree are you now feeling:	Energetic	0 O	1 O	2 O	3 O	4 O	5 O	6 O	7 O	8 O	9 O	10 O	Unenergetic
18. To what degree are you now feeling:	Patient	0 O	1 O	2 O	3 O	4 O	5 O	6 O	7 O	8 O	9 O	10 O	Impatient
19. To what degree are you now feeling:	Relaxed	0 O	1 O	2 O	3 O	4 O	5 O	6 O	7 O	8 O	9 O	10 O	Tense
20. To what degree are you now feeling:	Exhilarated	0 O	1 O	2 O	3 O	4 O	5 O	6 O	7 O	8 O	9 O	10 O	Depressed
21. To what degree are you now feeling:	Able to concentrate	0 O	1 O	2 O	3 O	4 O	5 O	6 O	7 O	8 O	9 O	10 O	Unable to concentrate
22. To what degree are you now feeling:	Able to remember	0 O	1 O	2 O	3 O	4 O	5 O	6 O	7 O	8 O	9 O	10 O	Unable to remember
23. To what degree are you now feeling:	Able to think clearly	0 O	1 O	2 O	3 O	4 O	5 O	6 O	7 O	8 O	9 O	10 O	Unable to think clearly

24. Overall, what do you believe is most directly contributing to or causing your fatigue?

_____

25. Overall, the best thing you have found to relieve your fatigue is:

_____

_____

26. Is there anything else you would like to add that would describe your fatigue better to us?

_____

_____

27. Are you experiencing any other symptoms right now?

O No O Yes (*please describe*)_____

_____

If you need more space, please continue below and include the item number:

MSA

We have listed 24 symptoms below. Please read each one carefully. If you had the symptom during the past week, let us know how OFTEN you had it, how SEVERE it was usually and how much it DISTRESSED OR BOTHERED you by circling the appropriate number. If you DID NOT HAVE the symptom, make an X in the box marked "DID NOT HAVE".

DURING THE PAST WEEK Did you have any of the following symptoms?	DID NOT HAVE	IF YES How OFTEN did you have it?				IF YES How SEVERE was it usually?				IF YES How much did it DISTRESS or BOTHER you?				
		Rarely	Occasionally	Frequently	Almost Constantly	Slight	Moderate	Severe	Very Severe	Not at all	A Little Bit	Somewhat	Quite a Bit	Very Much
Difficulty concentrating	O	O	O	O	O	O	O	O	O	O	O	O	O	O
Pain	O	O	O	O	O	O	O	O	O	O	O	O	O	O
Lack of energy	O	O	O	O	O	O	O	O	O	O	O	O	O	O
Cough	O	O	O	O	O	O	O	O	O	O	O	O	O	O
Feeling nervous	O	O	O	O	O	O	O	O	O	O	O	O	O	O
Dry mouth	O	O	O	O	O	O	O	O	O	O	O	O	O	O
Nausea	O	O	O	O	O	O	O	O	O	O	O	O	O	O
Feeling drowsy	O	O	O	O	O	O	O	O	O	O	O	O	O	O
Numbness/tingling in hands/feet	O	O	O	O	O	O	O	O	O	O	O	O	O	O
Difficulty sleeping	O	O	O	O	O	O	O	O	O	O	O	O	O	O
Feeling bloated	O	O	O	O	O	O	O	O	O	O	O	O	O	O
Problems with urination	O	O	O	O	O	O	O	O	O	O	O	O	O	O
Vomiting	O	O	O	O	O	O	O	O	O	O	O	O	O	O
Shortness of breath	O	O	O	O	O	O	O	O	O	O	O	O	O	O
Diarrhea	O	O	O	O	O	O	O	O	O	O	O	O	O	O
Feeling sad	O	O	O	O	O	O	O	O	O	O	O	O	O	O
Sweats	O	O	O	O	O	O	O	O	O	O	O	O	O	O
Worrying	O	O	O	O	O	O	O	O	O	O	O	O	O	O
Problems with sexual interest or activity	O	O	O	O	O	O	O	O	O	O	O	O	O	O
Itching	O	O	O	O	O	O	O	O	O	O	O	O	O	O
Lack of appetite	O	O	O	O	O	O	O	O	O	O	O	O	O	O
Dizziness	O	O	O	O	O	O	O	O	O	O	O	O	O	O
Difficulty Swallowing	O	O	O	O	O	O	O	O	O	O	O	O	O	O
Feeling irritable	O	O	O	O	O	O	O	O	O	O	O	O	O	O

MSA

We have listed 8 symptoms below. Read each one carefully. If you have had the symptom during this past week, let us know how SEVERE it was usually and how much it DISTRESSED or BOTHERED you by circling the appropriate number. If you DID NOT HAVE the symptom, make an "X" in the box marked "DID NOT HAVE."

DURING THE PAST WEEK Did you have any of the following symptoms?	DID NOT HAVE	IF YES How SEVERE was it usually?				IF YES How much did it DISTRESS or BOTHER you?				
		Slight	Moderate	Severe	Very Severe	Not at all	A Little Bit	Somewhat	Quite a Bit	Very Much
Mouth sores	O	O	O	O	O	O	O	O	O	O
Change in the way food tastes	O	O	O	O	O	O	O	O	O	O
Weight loss	O	O	O	O	O	O	O	O	O	O
Hair loss	O	O	O	O	O	O	O	O	O	O
Constipation	O	O	O	O	O	O	O	O	O	O
Swelling of arms or legs	O	O	O	O	O	O	O	O	O	O
"I don't look like myself"	O	O	O	O	O	O	O	O	O	O
Changes in skin	O	O	O	O	O	O	O	O	O	O

IF YOU HAD ANY OTHER SYMPTOMS DURING THE PAST WEEK, PLEASE LIST BELOW AND INDICATE HOW MUCH THE SYMPTOM HAS DISTRESSED OR BOTHERED YOU.

	Not at all	A Little Bit	Somewhat	Quite a Bit	Very Much
Other: _____	O	O	O	O	O
Other: _____	O	O	O	O	O
Other: _____	O	O	O	O	O

CURRICULUM VITAE

HOME
1105 W NC Highway 54 Bypass Apt. A4
Chapel Hill, NC 27516
Phone: (919) 286-0411 ext. 5526

OFFICE
Department of Psychiatry
Duke University

E-mail: eric.dedert@duke.edu

EDUCATION

University of North Carolina Aug. 2006-Aug. 2007
Chapel Hill, NC
Clinical Psychology Intern – Behavioral Medicine emphasis

University of Louisville Aug, 2001- present
Louisville, KY
Doctoral Student Clinical Psychology program

Indiana University Aug. 1995-Dec. 1998
Bloomington, IN
Bachelor of Science
Major: Psychology
Minor: Business

Purdue University Aug. 1994-Dec.1994
West Lafayette, IN

EMPLOYMENT

Duke University Aug. 2007-present
Department of Psychiatry
Position: Postdoctoral Research Fellow
Responsibilities: Conduct research into optimizing smoking cessation interventions and provide clinical service

University of North Carolina Hospitals Aug. 2006-Aug. 2007
Department of Psychiatry
Position: Clinical Psychology Intern – Behavioral Medicine emphasis

University of Louisville July 2006-Aug. 2006
Department of Psychological and Brain Sciences
Position: Instructor
Responsibilities: Taught undergraduate course in statistics and research design. Prepared lesson plan, lecture materials, homework problems, and exams.

University of Louisville Aug. 2001-May 2002
Department of Psychological and Brain Sciences Aug. 2005-May 2006
Position: Graduate Teaching Assistant
Responsibilities: Taught introduction to psychology classes to undergraduate students. Prepared lesson plan for lab sections.

Brown Cancer Center Aug. 2003-June 2005
Louisville, KY
Position: Project Director
Responsibilities: Directed project investigating psychosocial issues in patients with lung cancer. My duties included the preparation of measures for data collection, statistical consultation on grant submission, recruitment, interviewing participants, data management, training of other research personnel, and preparation of human subjects reports and proposals. This project is currently in the results dissemination phase.

Central State Hospital Aug. 2002-May 2003
Louisville, KY
Position: Research Assistant
Responsibilities: Addressed clinical questions by designing archival studies of patient charts, and writing reports based on data collected. Chart reviews ensuring compliance with documentation guidelines.

Indiana University Feb. 2001-May 2001
Social Psychology Research Laboratory
Bloomington, IN
Position: Research Assistant
Responsibilities: Contacted research participants, collected data, entered data.

Stone Belt Center Mar. 1999-July 2001
Bloomington, IN
Position: Behavior Technician
Responsibilities: Provided active treatment to developmentally disabled adolescent males. Initiated behavior tracking forms in charts and ensured reliable tracking by staff. Met with house staff regarding behavior plan revisions and submitted proposed revisions to Behavioral Specialist.

RESEARCH PROJECTS

Transplant Outcomes Research Aug. 2006-present
Intern for Dr. Eileen Burker working clinically with patients being evaluated as candidates for heart and lung transplants. This research focuses on psychosocial predictors of medical and quality of life outcomes in transplant recipients. My responsibilities include human subjects proposals, recruitment, chart review, and manuscript preparation. I am currently collaborating with Dr. Burker and other researchers on a review of post-transplant employment in heart transplant recipients and

an analysis of pre-transplant depression as a predictor of post-transplant survival in lung transplant recipients.

Biobehavioral Research Group Aug. 2001-present
Research Assistant for Dr. Sandra Sephton, Dr. Paul Salmon, and Dr. Jamie Studts. A project investigating a Mindfulness-Based Stress Reduction (MBSR) intervention and psychosocial factors in the adjustment of women with fibromyalgia has been completed. My duties have included data management, data analysis, and preparations of portions of the study results for journal publication.

A project investigating psychosocial factors in the adjustment of patients with lung cancer is currently in the data analysis and dissemination of results phase. My duties have included the preparation of measures for data collection, recruitment, interviewing participants, data management, training of other research personnel, and preparation of human subjects reports and proposals.

My dissertation is investigating the effects of distress and coping on circadian physiological rhythms in women with breast cancer. This project is in the data collection phase.

Cognitive Psychology Research Lab Aug. 1998-Dec. 1998
Undergraduate Research Assistant for Dr. Jerome Busemeyer at Indiana University. The primary research was in decision field theory. My duties included scheduling participants and conducting experiments.

PRACTICA/PREDOCTORAL CLINICAL EXPERIENCE

Psychological Services Center Aug. 2001-May 2006
Department of Psychological & Brain Sciences
University of Louisville
Louisville, KY
Supervisors: Abbie Beacham, PhD, Tamara Newton, PhD, Amy Buckley, PhD, Paul Bock, PhD, & Bernadette Walter, PhD
Provided cognitive-behavioral therapy (CBT) to primarily low-income clients. Clinical team concentrations included problem-focused health psychology and women with a history of trauma. Provided assessment including Attention Deficit/Hyperactivity Disorder (ADHD), developmental disability, advanced placement, and full diagnostic cases.

Ambulatory Internal Medicine Clinic Jan. 2003-May 2005
Department of Psychological & Brain Sciences
University of Louisville
Louisville, KY

Supervisors: Abbie Beacham, PhD & Amy Buckley, PhD

Provided cognitive-behavioral therapy (CBT) to primarily low-income clients in a primary care setting. Services included brief assessments and interventions focused on behavioral health, medical regimen adherence, pain management, and depression and anxiety reduction.

Christopher East Health Care Facility Aug. 2003-July 2004
Louisville, KY
Supervisor: D. Bradley Burton, PhD

Provided neuropsychological assessments of patients in acute rehabilitation from traumatic brain injury.

AWARDS AND MEMBERSHIPS

"Distress and Immune Activation in Lung Cancer" cited by the Society of Behavioral Medicine as a Meritorious Student Poster at 2005 meeting.

Society of Behavioral Medicine, Student Member, 2002 - 2003, 2004-present

Grawemeyer Summer Research Stipend, 2002, 2003, 2005

International Congress on Psychosomatic Medicine, Student Member, 2003-2004

"Sense of coherence in women with fibromyalgia is enhanced by a Mindfulness-Based Stress Reduction Program" cited in Clinician's Research Digest: Briefings in Behavioral Science 21(7), July 2003. Paper selected as among those representing the "most critical research to bring to the attention of clinicians".

GRANT PROPOSALS SUMITTED

Intramural Research Incentive Grants, Research on Women Grant awarded to fund dissertation, June 2005.

Department of Defense Breast Cancer Research Program Predoctoral Grant, submitted May 2004 and not funded.

JOURNAL PEER REVIEW

Journal of Psychosomatic Medicine
Nicotine & Tobacco Research
Journal of Clinical Psychopharmacology
Journal of Traumatic Stress

PUBLICATIONS

Weissbecker, I, Floyd, A, Dedert, E, Salmon, P, and Sephton, S. Childhood trauma and diurnal cortisol disruption in fibromyalgia syndrome (2006). *Psychoneuroendocrinology*, 31, 312-324.

Dedert, E., Studts, J., Weissbecker, I., Salmon, P., Banis, P., & Sephton, S. (2004). Religiosity may help preserve the cortisol rhythm in women with stress-related illness**.** *International Journal of Psychiatry in Medicine*, 34(1), 61-77.

Weissbecker, I., Salmon, P., Studts, J., Floyd, A., Dedert, E., & Sephton, S. (2002). Sense of coherence in women with fibromyalgia is enhanced by a Mindfulness-Based Stress Reduction Program. *Journal of Clinical Psychology in Medical Settings*, 9(4); 297-307.

NATIONAL PRESENTATIONS

Martin, M., E. Lush, E. Dedert, A. Chagpar, P. Rhodes, S. Sephton (2007). Avoidant coping styles: Associations with physiological stress markers among recently diagnosed breast cancer patients. Poster presented at Louisville Breast Cancer Update, Louisville, KY.

Dedert, E., Ghate, S., Floyd, A., Banis, P., Weissbecker, I., Hermann, C. Studts, J., Salmon, P. and Sephton, S. (2005). Distress and Immune Activation in Lung Cancer. Poster presented at the meeting of the Society of Behavioral Medicine, March 2005, cited as Meritorious Student Poster.

Sephton, S.E., Weissbecker, I., Floyd, A., Dedert, E., and Salmon, P. Childhood trauma and diurnal cortisol disruption in fibromyalgia syndrome. Poster presented at the annual meeting of the American Psychosomatic Society, Vancouver, British Columbia, Canada, March 2-5,
2005.

Dedert, E., Ghate, S., Floyd, A., Banis, P., Weissbecker, I., Hermann, C. Studts, J., Salmon, P. and Sephton, S. Spirituality Buffers Symptom Distress in Patients with Lung Cancer. Poster presented at the 17th World Congress on Psychosomatic Medicine, Waikoloa, HI, August 23-28, 2003.

Weissbecker, I., Ghate, S., Studts, J., Floyd, A., Dedert, E., and Sephton, S. Gender Differences in the relationship between social support and psychological distress in lung cancer patients. Psychosomatic Medicine 66(1), A-36. Poster presented at the 17th World Congress on Psychosomatic Medicine, Waikoloa, HI, August 23-28, 2003.

Weissbecker, I., Dedert, E., Studts, J., Salmon, P., and Sephton, S. (2003). Traumatic Events and Health in Women with Fibromyalgia. Poster presented at the 17th World Congress on Psychosomatic Medicine, Waikoloa, HI, August 23-28, 2003.

Weissbecker, I., Ghate, S., Dedert, E., Floyd, A., Studts, J., Salmon, P., Banis, P., & Sephton, S. Gender Differences in the relationships between psychological distress and social support in lung cancer patients. Poster presented at the Conference of the American Psychosomatic Society (APS), March 2003.

Beacham, A., Stetson, B., Newton, T., Ulmer, C., Dedert, E., Weissbecker, I., Mitchell, C. & Woodruff-Borden, J. Are we adequately fostering medically underserved patients' interest in health-enhancing information and self-management? Poster presented at the meeting of the Society of Behavioral Medicine, March 2003.

Dedert, E., Banis, P., Weissbecker, I., Salmon, I., Studts, J., & Sephton, S. Spiritual Expression is Linked with and Immune Function Among Women with Fibromyalgia. Annals of Behavioral Medicine, 24 (2002 Suppl.), S080, March, 2002

DESCRIPTION

I am a postdoctoral research fellow at Duke University. My doctoral degree will be conferred from the University of Louisville in December of 2007. My clinical training has focused on brief, problem-focused mental and behavioral health interventions in underserved groups with chronic illness. I plan to do clinical research in these groups and am currently an active researcher with the Nicotine Research Lab at Duke University and the Durham, NC VA and the Biobehavioral Research Lab at the University of Louisville.