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The Impact of Breast Cancer Screening on Sleep, Affect, and Immune Functioning

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The Impact of Breast Cancer Screening on Sleep, Affect, and Immune Functioning

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Abstract

Despite great strides that have been made over the past several decades in terms of diagnosis and treatment, breast cancer remains the most commonly diagnosed cancer in American women and the second leading cause of cancer-related mortality for women in the United States. Although the benefits of early detection of breast cancer have been clearly established, the advantages of screening must also be weighed against a potential corresponding negative psychological impact of screening procedures. The purpose of the present study was to further investigate the impact of breast cancer screening on previously unstudied or understudied aspects of psychological and physiological health, including sleep quality, negative and positive affect, and biomarkers of immune system response and to explore between-group differences in these markers based on diagnostic status over the course of time between surgical consult and diagnosis following breast biopsy. Results indicated substantially impaired sleep quality as well as elevations in negative affect across the study sample. Higher levels of a biological marker of inflammation were shown to be associated with poorer sleep quality. Positive and negative affect were also associated in the study sample, which is thought to be indicative of a high level of emotional activation during breast cancer screening and diagnosis. Counter to study hypotheses, results indicated neither improvements in sleep quality or affect nor decreased levels of serum cytokines were noted in women who received a benign diagnosis. Conversely, results for several scales indicated improved sleep quality for women diagnosed with breast cancer relative to women who received a benign diagnosis, providing support for the argument that it is the experience of uncertainty that leads to the acute psychological distress consistently shown in women undergoing breast cancer screening and breast biopsy.

During the past several decades, breast cancer has emerged as one of the most widely researched and most publicly supported areas within the broader field of oncology. However, despite great strides that have been made in terms of diagnosis and treatment, breast cancer remains the most commonly diagnosed cancer in American women and the second leading cause of cancer-related mortality for women in the United States (Ferrante, Chen, & Kim, 2008). It is estimated that approximately 1 in every 8 American women will be treated for breast cancer at some point during her lifetime and that roughly 1 in every 30 of these women will die as a result of this disease (American Cancer Society, 2002). As is true for many cancers, the incidence of breast cancer increased as women grow older, and despite progress in terms of research into environmental and behavioral risk factors, most cases of breast cancer will occur in women that do not present with identified predictors of the disease (Colditz, Willett, Hunter, Stampfer, Manson, & Hennekens, 1993; Seidman, Stellman, & Mushinski, 1982; Strax, 1987). As risk factors alone are not sufficient to identify individuals that are likely to develop breast cancer, early identification and screening efforts have increased over the past decade. According to the American Cancer Society (2009), in excess of one million women received a breast diagnostic evaluation (most commonly mammography) in the United States in 2008, with approximately 180,000 resulting in breast cancer diagnosis (Montgomery, 2010).

The purpose of breast cancer screening is to allow for detection of the disease or of disease risk factors to allow for early therapeutic interventions and/or preventative measures, as research has shown treatments are more effective when the disease is diagnosed at an early stage (Wardle & Pope, 1992). Since comprehensive breast cancer

screening was first implemented, research has shown that biannual mammography is the most effective method for reducing mortality in women 50 years or older (Kerlikowske et al., 1995). Studies have shown substantial reduction in mortality rates among the general population of women in this age group following the introduction of biannual mammography into common practice (Absetz, Aro, & Sutton, 2003; deKoning, 2000). Two large scale controlled mammography trials conducted in Scandinavia (Tabar, Fagerbery, Duffy, & Day, 1989) and in North America (Shapiro, 1977) demonstrated greater than 30% reductions in breast cancer mortality as a result of screening.

The utility of breast cancer screening is only achieved if mammography examinations are administered frequently to large numbers of women throughout the general population. Such widespread implementation of mammography screening results not only in a great number of negative tests but also a considerable occurrence of false-positive or inconclusive test results that require additional follow-up examination (Andrykowski et al., 2002). Some studies have suggested that roughly 12 women receive false-positive diagnosis for every one correctly identified case of breast cancer (Wardle & Pope, 1992). Medical follow-up for an abnormal mammography commonly involves either repeat mammography exam or the more invasive breast biopsy. Research suggests that more than 80% of breast biopsies conducted following abnormal mammography result in benign diagnosis and exponentially higher numbers of benign diagnoses after repeat mammogram (Skrabanek, 1985). According to Elmore and colleagues (1998) if ten screening mammograms were conducted in a woman over 50, there would be up to a 75% chance that one false-positive outcome would result. As breast cancer is less prevalent in younger women, the percentage of false-positive diagnoses would likely

increase for women under 40 years of age. As predicted by Lerman and Rimer (1995), if 40% of American women over the age of 40 were to undergo mammography screening, greater than three million would receive false positive or indeterminate results.

Although the benefits of early detection of breast cancer have been clearly established, the advantages of screening must also be weighed against a potential corresponding negative psychological impact that might result from participation in screening procedures even when a malignancy is not identified (Lerman, Rimer, & Engstrom, 1991; Wardle & Pope, 1992). Although diagnostic and curative breast cancer surgeries are conducted out of medical necessity, these procedures have been shown by to result consistently in significantly heightened distress (e.g. Deane & Degner, 1998; Ganz, Schag, Lee, Polinsky, & Tan, 1992; Montgomery, Weltz, Seltz, & Boybjerg, 2002). News of an abnormal mammogram is a stressful event that has the potential to increase individual vulnerability to psychological and physical illness by activating or intensifying pre-existing psychological issues (Alderete, Juarbe, Kaplan, Pasick, & Perez-Stable, 2006; Brilman & Ormel, 2001). Potential costs of screening vary from trauma resulting from the identification of disease in symptom-free individuals to increased psychological stress and anxiety in healthy individuals that receive a false-positive diagnosis (Wardle & Pope, 1992). There is also a real monetary cost for screening. For every $100 spent on breast cancer screening, an estimated $33 will be spent on tests that will lead to a false-positive result (Humphrey, Helfand, Chan, & Woolf, 2002).

Mammography screening has been shown to result in both short-term distress and anxiety for women with false positive diagnoses (Aro et al., 2000; Brett et al., 1998) and long term effects such as perceived increased risk for future diagnosis of breast cancer

(Aro et al., 2000). The acute psychological distress reported might be due to the prospect of a grave diagnosis, fear of potential cancer treatment, the procedure of the screening itself which often involves uncomfortable and invasive testing procedures, as well as a waiting period before definitive diagnosis is made, and/or anxiety around the experience of a painful and untimely death (Koller, Kussman, & Lorenz, 1996; Wardle & Pope, 1992). Many studies have been conducted concerning breast cancer screening behavior as well as the psychological impact of a positive cancer diagnosis, but only a handful of studies have focused on the effects of cancer screening itself resulting in the notification of a benign diagnosis. One study by Deane and Denger (1998) found that women who had received a benign diagnosis after breast biopsy demonstrated continued heightened anxiety and perceived uncertainty relative to those who received a positive breast cancer diagnosis even after they were informed of their test results. The experience of breast biopsy appears to be particularly impactful. Lindfors and colleagues (1998) found that women who had undergone breast biopsy with benign results reported substantially greater levels of distress and anxiety than those who had received a benign diagnosis after repeat mammogram. Another study involving a small group of women that had recently undergone benign breast biopsy after abnormal mammogram found that 5 of the 30 women described the experience as the worst event that had occurred in their lives up to that time (Gram, Lund, & Slenker, 1990), and two women involved in a retrospective study by Weil and Hawker (1997) reportedly committed suicide after receiving notice of abnormal mammogram results.

Overall, a sound body of research shows that a significant number of women that receive a false-positive mammography test result will experience some adverse

psychological impact (Lipkus, Halabi, Stirigo, & Rimer, 2000). Most commonly noted are increased levels of anxiety, intrusive thoughts around breast cancer, and symptoms of depression (Pisano, Carp & Gallant, 1998). Elevated levels of anxiety, depression, and other negative emotions have been found to endure for up to five years after receipt of an abnormal breast cancer screening result (Lipkus et al., 2000; Pisano et al., 1998). Evidence has also been found that anticipatory distress occurring in the days or weeks prior to breast biopsy or lumpectomy is associated with post-surgical side-effects, including increased chance of infection and psychological symptoms including depression and anxiety (Montgomery & Bovbjerg, 2004).

One explanation that has recently been put forth for the negative psychological impact of breast cancer screening, even when no malignancy is identified, involves the level of uncertainty that characterizes the screening process (Montgomery, 2010). Uncertainty in terms of illness has been defined as the inability of an individual to discern the meaning of an illness-related occurrence and an inability to ascertain an accurate prediction of likely outcomes (Montgomery, 2010). This set of circumstances results in an infringement on a woman's belief in herself as healthy and leads her to face the possibility of her own mortality (Jordens, Little, Paul, & Sayers, 2001). Before receiving a benign or positive diagnosis for breast cancer, women experience a sometimes extended period of uncertainty as the await breast biopsy results. Despite advances in rapidity of diagnosis, Ferrante and colleagues (2008) have noted an average length of time interval from discovery of an abnormal breast mass to definitive diagnosis ranges from 4-6 weeks. Further supporting uncertainty as an important factor in the distress involved in breast cancer screening, several studies have reported lower levels of distress when

communication of results is more rapid, waiting times between tests shorter, and referral to surgery occurs expeditiously (Barton et al., 2004; Ferrante et al., 2008). The degree of uncertainty that occurs during the diagnostic process is heightened by the fact that the initial test, mammography, will confirm that breast cancer is possible but does not immediately determine whether or not a malignancy is present (Andrykowski et al., 2002).

The majority of published studies that have explored distress during breast cancer screening have noted the presence of anxiety and distress as persisting through the diagnostic phase, only resolving when definitive diagnosis is received. Interestingly, levels of distress decrease following diagnosis, even when the diagnosis received indicates malignancy (Deane & Degner, 1998; Fridfinnsdottir, 1997; Shaw, Wilson, & O'Brien, 1994). Levels of anxiety in women during the period of uncertainty before diagnosis are equivalent to those noted among patients admitted to in-patient psychiatric units for treatment of acute anxiety disorders (DeKeyser, Wainstock, Rose, Converse, & Dooley, 1998; Scott, 1983). Concern around the psychological effects of uncertainty during breast cancer screening has increased since the introduction of broad screening programs. The experience of breast cancer screening has been reported as negatively impacting treatment outcomes in women diagnosed with the disease (Thorne, Harris, Hislop, & Vestrup, 1999), and also impact behavioral changes in women that receive a benign diagnosis, including reduced likelihood that these women will comply with future screening recommendations (Andrykowski et al. 2002; Barton et al., 2004; Brett, Austoker, & Ong, 1998; Haas, Kaplan, McMillan, & Esserman, 2001; Lampic, Thurfjell, Bergh, & Sjoden, 2001; Lowe, Balanda, Del Mar, & Hawes, 1999; Olsson, Armelius,

Nordahl, Lenner, & Westman, 1999). One study, conducted by Schnur and colleagues (2008), found increased levels of psychological distress in women scheduled for breast biopsy relative to a group of women scheduled for lumpectomy, which is a much more invasive procedure that can result in substantial breast tissue loss. The authors believe that the increased level of uncertainty involved in breast biopsy, where diagnosis and need for future treatment are unknown, relative to lumpectomy, was responsible for this unexpected finding (Schnur et al., 2008). In another study also conducted by Schnur and colleagues (2005) levels of psychological distress in pre-biopsy patients were noted to be higher than those found in a sample of women following definitive diagnosis of metastatic breast cancer.

The evidence for the negative impact of breast cancer screening is not uniform and a number of studies examining the impact of false-positive cancer screening (abnormal mammogram followed by normal breast biopsy) have shown negative psychological effects to be neither severe nor persistent (Lerman et al., 1991; Wardle, Pernet, Collins, & Bourne, 1994). Other researchers have shown that some psychological characteristics, such as active coping and social support, are positively related to well-being in women with false-positive breast cancer screening results, which provides some indication that buffering effects might be possible (Blutton, Pakenham, & Buckley, 1999).

The majority of the literature concerned with the effects of breast cancer screening is not only methodologically limited, as these studies often use self-report measures that are retrospective in nature, but prior research has also been limited in terms of the psychological and behavioral characteristics that have been assessed. State and

trait anxiety, depression, and breast-cancer specific worry have been the most common focal points, with some studies identifying heightened levels of these constructs and some failing to find differences between women undergoing breast cancer screening and control samples (Ekeberg et al., 2001). While prior research has examined the impact of breast cancer screening on specific aspects of mood/affective state, primarily depression and anxiety, and behavior in terms of coping strategies, none to date have been conducted that explore a more balanced mood profile, including both positive and negative affect, or that examine the impact of screening on specific daily behaviors, such as sleep, commonly effected by stress. In addition, although prior research has shown a clear profile of immune system changes following breast cancer treatment (Lutgendorf, 2009; Sepah & Bower, 2009), few studies have explored the potential impact of the breast cancer screening process on biological markers of immune system functioning. One possible explanation for the variability of findings evidenced in the literature is that the measures commonly included in test batteries are not picking up effects specific to the short-term experience of acute stress that characterizes breast cancer diagnostic screening.

Although a great deal of support has been shown for the increased prevalence of depressed mood, anxiety, and chronic stress in patients undergoing treatment for breast cancer (eg. Gram et al., 1990; Koller, Kussman, & Lorenz, 1996; Pisano et al., 1998), it is possible that the impact of screening and diagnosis is manifesting across a broader profile of symptoms. In order to investigate this possibility, the present study seeks to examine the impact of breast cancer screening and early diagnosis on several constructs known to impact in patients undergoing treatment for breast cancer that have been widely

understudied in women undergoing breast cancer screening. These include sleep quality, mood state in terms of both positive and negative affect, and immune system functioning. To date, only one published study has investigated immune system (DeKeyser, Wainstock, Rose, Coinverse, & Dooley, 2004) functioning during breast cancer screening in women that will go on to receive both benign and positive diagnoses, and a recent review of the literature has not identified a single published study examining the impact of breast cancer screening on sleep or negative and positive affect.

Sleep and Affect. At the National Institute of Health State of the Science conference (NIH, 2004), sleep and mood disturbance were identified as the most frequently occurring and debilitating symptoms of cancer and cancer treatments. Sleep quality has been shown to impact reported symptoms of fatigue, pain tolerance and severity, and immune system functioning; poor sleep has been related to symptoms of depression and anhedonia (Dickstein & Moldofsky, 1999; Sheev, 1996; Irwin, 2002). Although the impact of breast cancer screening on sleep quality and quantity has not been fully explored to date, problematic sleep has been established as a significant issue for cancer patients and is often the target of pharmacological intervention as a part of adjuvant cancer treatment (Derogatis, Feldstein, & Morrow, 1979; Goldberg & Mor, 1985). Although figures have varied widely, the overall prevalence of significant sleep disturbance in cancer patients has been estimated to be as high as 95% (Thomas, 1987). While the number of studies that have investigated the rates of sleep disturbance in women suffering from breast cancer is limited, the existing literature notes that these patients frequently report unsatisfactory sleep and experience sleep problems, including

frequent awakenings, while undergoing chemotherapy or radiation treatment (Carpenter & Andrykowski, 1998; Berger, 1995; Berger, 1998; Berger & Farr, 1999; Knobf, 1986)

One study found a high percentage of sleep disturbance in a sample of women undergoing treatment for breast cancer and also demonstrated that these sleep problems predicted lower self-reported quality of life (Fortner, Stepanski, Wang, Kasprowicz, & Durrence, 2002). The authors also noted that while patients that were currently undergoing treatment for breast cancer (radiation or chemotherapy) showed a trend toward greater sleep disturbance, that levels of sleep disturbance in these patients was not higher than in those that were not currently undergoing treatment. This would suggest that sleep problems in cancer patients are not entirely due to the negative effects of radiation and chemotherapy treatments. One possible explanation for this finding might be that the sleep issues reported by cancer patients might be due in part to psychological factors, such as stress, anxiety, or depression, that have been shown to impact sleep quality in otherwise physically healthy individuals (Fortner et al., 2002; Lutgendorf & Costanzo, 2003; Spiegel & Sephton, 2001; Antoni, 2003).

Importantly, several investigators have cited changes in sleep quality as early symptoms of a broader pattern of systemic dysregulation. Dysregulation of several interconnected circadian systems has been demonstrated in women with breast cancer, including the adrenal system, the stress response system, and the autonomic nervous system, which is responsible in part for sleep regulation (Bovbjerg, 2003; Sephton and Spiegel, 2003; Touitosu, Bogdan, Levi, Benavides, & Auzeby, 1996). Dysfunction across these symptoms has also been shown to be associated with a more rapid course of disease progression in some cases (Bovbjerg, 2003; Sephton and Spiegel, 2003; Touitosu

et al., 1996). Other factors, such as high levels of stress and psychological disorders such as depression, may contribute to disruption of normal circadian rhythms and might therefore indirectly contribute to shorter survival time in breast cancer patients (Antoni, 2003; Carlson, Campbell, Garland, & Grossman, 2007; Lutgendorf & Costanzo, 2003; Spiegel & Sephton, 2001). Therefore, changes in sleep pattern and/or sleep quality might provide a useful marker of risk for disruption of normal circadian rhythm and comorbid psychological symptomology. As sleep quality is also related to psychological factors such as anxiety and depression, it is possible that sleep disturbance or changes in sleep quality might be evident in women undergoing breast cancer screening even if symptoms of depression and anxiety are not detectable.

Mood disturbance has also been noted in non-cancer populations as associated with multiple physical, immunological, and psychological changes, including increased reported severity of pain, increased levels of pro-inflammatory cytokines, and increased symptoms of depression (Bardwell et al., 2006; Lee et al., 2004; Weitzner et al., 1997). Approximately 20-40% of women with breast cancer experience and report experiencing mood disturbances at some point during the course of treatment (Badger et al., 2004). Although several studies have found support for increased symptoms of subjective distress, most commonly measured via assessment of depression or anxiety, in women undergoing breast cancer screening, results have been inconsistent (e.g., Ekeberg et al., 2001).

In order to further explore mood disturbance in women in the diagnostic phase of breast cancer treatment, the present study will explore the impact of screening and diagnosis on levels of self-reported positive and negative affect. Positive and negative

affect are commonly described as independent constructs that represent separate but related components of mood state (Watson, Clark, & Tellegen, 1999). Positive and negative affect are representative of dimensional mood states with high negative affect characterized by the experience of subjective distress and unpleasurable engagement while positive affect represents subjective feelings of satisfaction and pleasurable engagement with one's environment (Watson & Clark, 1984). High levels of positive affect have been associated with high energy, extraverted behavior, improved concentration, and emotions such as enthusiasm and alertness, and low levels of positive affect are related to feelings of sadness, disengagement, and lethargy (Crawford & Henry, 2004). Alternatively, high negative affect is related to neuroticism, anxiety, and the emotional experience of guilt, anger, fear and nervousness, while low negative affect is related to feelings of calmness, relaxation, and serenity (Crawford & Henry, 2004). By including measures of both positive and negative affect in the present study, we hope to not only discern the presence of negative emotional activation but also to examine the impact of breast cancer screening on positive emotional activation, an area that has to date remained unexplored.

Immune System Markers. As was discussed above, individuals suffering from chronic illnesses, including cancer, often exhibit diverse psychological symptomology including fatigue, anxiety, and depression (e.g., McDaniel, Musselman, Porter, Reed, & Nemeroff, 1995). Although the traditional method for assessment of psychological symptoms has been via self-report questionnaire or interview-based measures, prior clinical research suggests a strong relationship between disease related inflammation and depression in patients suffering from chronic illnesses, including diabetes, obesity, and

coronary heart disease (Frasure-Smith & Lesperance, 2006). Support for this relationship has led researchers over the past two decades to explore measurement of biological markers of immune-related inflammation as a non-self-report technique for assessing level of psychological and physiological distress (Glaser, Robles, & Sheridan, 2003; Konsman, Parnet, & Dantzer, 2002; Reichenberg, Yirmiya, & Schuld, 2001). Inflammatory cytokines are one such biological marker.

Cytokines are known to function as signaling molecules that are related to the regulation of cellular inflammation and are produced by cells that regulate the human immune response (Thomson & Lotze, 2003). While multiple classification systems for cytokines have been developed, these molecules are largely divided into two distinct groups: cytokines that promote inflammation, termed pro-inflammatory cytokines, and those that reduce inflammation, referred to as anti-inflammatory cytokines (Dinarello, 2000). Pro-inflammatory cytokines are particularly important in terms of their role in communication of immune activity to the central nervous and neuroendocrine systems (Reichlin, 1993). For example, when an infection is present somewhere in the body, immune regulating cells release pro-inflammatory cytokines which act by signaling for increased pituitary and adrenocortical secretions to combat pathogens (Blalock, 1989).

Unfortunately, pro-inflammatory cytokines are also involved with chronic inflammation which has been associated with greater morbidity of diseases including cardiac disease, cancer, and diabetes (Black, 2003). Chronic inflammation has also been noted as a contributing factor in cancer proliferation and has been associated with mortality in breast cancer patients (Hagemann et al., 2007; Pierce et al., 2009). More positive factors such as positive affect and social support have been associated with

decreased levels of proinflammatory cytokines (Chida & Steptoe, 2008; Rhyff et al., 2004). Long term exposure to high concentrations of stress hormones instigates an immune system response that diminishes the immune system's ability to respond to the body's anti-inflammatory actions, resulting in higher levels of pro-inflammatory cytokines. (Miller, Cohen, & Richey, 2002). Although few studies have assessed levels of pro-inflammatory cytokines in breast cancer patients, research has shown that positive affect in breast and prostate cancer patients is related to higher levels of inflammatory cytokines and Interleukin-6 (IL6), an endogenous cytokine, across multiple measurement time-points during a 6-week course of external beam radiation therapy (Seraph & Bower, 2009). In contrast, prior research has also indicated that cancer patients who are high in positive affect before treatment may have a more efficient inflammatory response, as reflected in higher levels of pro-inflammatory cytokines during treatment (Lutgendorf, 2009).

During the course of an illness, especially one characterized by prolonged symptoms such as breast cancer, depression and irritability are often reported as well as mild cognitive issues including impairment of attention, concentration, and short-term and working memory (Dantzer, O'Connor, Freund, Johnson, & Kelley, 2006). The symptoms commonly associated with sickness are in fact largely due to the body's immune response, which is characterized by changes in the autonomic and endocrine systems triggered by accessory immune cells and mediated by pro-inflammatory cytokines (including C-reactive protein and IL-6). C-reactive protein (CRP) is an acute phase protein that is associated with systematic inflammation in the body (American Heart Association, 2010). As was previously stated, pro-inflammatory cytokines

function by coordinating the body's local and systemic inflammatory response to pathogens in order to combat infectious agents. However, pro-inflammatory cytokines can also act on the brain and the periphery to cause sickness symptoms including fatigue and depression (Dantzer et al., 2006).

In the past decade, researchers have found that the immune response can cause not only symptoms associated with sickness but can also can result in psychological symptoms, including anxiety and depression, in physically ill individuals with no history of mental disorder (Dantzer et al., 2006). For individuals with cancer, a prolonged immune response to the presence of tumor cells leads to an overabundance of pro-inflammatory cytokines (Coussens & Werb, 2002). High levels of interleukin-6 (IL-6), a common circulating pro-inflammatory cytokine, have been associated with more negative outcomes in patients with breast cancer (Zhang & Anachi, 1999), and IL-6 is thought to stimulate increased tumor cell growth and to contribute to recurrence and metastasis of breast cancer (Balkwill & Mantovani, 2001; Leek & Harris, 2002). IL-6 has also been associated with disease stage progression in breast cancer (Rao, Dyer, Jameel, Drew, & Greenman, 2006). Pro-inflammatory cytokines have also been associated with symptoms of depression (Musselman et al., 2001) and fatigue (Bower et al., 2000) in breast cancer patients. Although elevated levels of proinflammatory cytokines have been related to increased rate of disease progression in cancer patients, the findings have been somewhat inconsistent (Lyon, McCain, Walter, & Schubert, 2008). Some studies have found differences in level of pro-inflammatory cytokines in breast cancer v. controls (Lyon et al., 2008) and some have not (Pusztai et al., 2004).

Although multiple studies have explored the involvement of pro-inflammatory cytokines in breast cancer, to our knowledge only one published study has investigated markers of immune function in women undergoing breast cancer screening. DeKeyser and colleagues (2004) looked at distress and immune function in women with suspected breast cancer. The authors reported associations between psychological distress, symptom distress, and levels of a serum cytokine, tumor necrosis factor alpha. However, the authors did not find differences in levels of cytokines between women with a benign diagnosis and women diagnosed with breast cancer (DeKeyser et al., 2004). In order to further explore immune system functioning in women undergoing breast biopsy and also to explore potential associations between immune markers, mood state, and sleep quality, the present study will involve measurement of two known immune response markers: IL-6 and CRP before and after breast biopsy.

Summary. Overall, prior research consistently suggests that the screening and early diagnostic phase of breast cancer treatment represents an acutely stressful experience for women. Several studies have noted increased symptoms of distress, depression and anxiety occurring during this time, with some studies reporting continued elevations in negative psychological symptoms persisting for months to years following even a benign diagnosis. One possible explanation for the distress that characterizes the diagnostic phase for breast cancer is the prolonged period of uncertainty experienced by women awaiting diagnosis via breast biopsy following abnormal mammogram. Although a substantial amount of research has explored depression, anxiety, social support and coping skills in women with suspected breast cancer, none to date have explored the impact of breast cancer screening on positive and negative affect or sleep quality. In

addition, only one published study to date has investigated levels of pro-inflammatory cytokines in women undergoing breast biopsy, and no study to date has explained the associations of these factors.

The purpose of the present study is to further investigate the impact of breast cancer screening by exploring changes in sleep, negative and positive affect, and biomarkers of immune system response, during the time between abnormal mammography and diagnosis following breast biopsy in a population of women with suspected breast cancer. As no prior research has involved an examination of sleep quality or negative and positive affect, the first primary aim of the present study is to determine if levels of sleep difficulty and affect are elevated in women with suspected breast cancer relative to normative samples. Then, we will explore potential relationships among study measures to determine if associations between serum cytokine levels, sleep quality, and affect are present in women undergoing breast cancer diagnostic testing. We will also explore any changes that might occur in terms of study variables before and after breast cancer diagnosis. Finally, the study sample will be split into two subgroups based upon diagnosis and potential between-group differences in sleep quality, affect, and immune markers will be examined.

Based upon prior research that has consistently reported increased psychological distress among women with suspected breast cancer, we expect that our study sample will demonstrate decreased sleep quality, decreased positive affect, and increased negative affect relative to normative PSQI and PANAS scale scores. We also expect that these elevations will decrease post-biopsy for the benign diagnosis group but will remain stable for those diagnosed with breast cancer. Elevations in serum cytokine levels are also

expected to increase during the pre- to post-biopsy period for both groups due to the stressful nature of the experience of breast cancer diagnostic testing. Finally, we expect to find associations between sleep quality, affect, and immune markers for both the benign diagnosis and positive breast cancer diagnosis groups.

Method

Participants and Procedure. Participants for this study were a convenience sample taken from a group of 100 consecutive patients who have been referred to the surgeons of the Neag Comprehensive Cancer Center for evaluation. The study sample consisted of women from 20-80 years of age who have been referred for follow up evaluation after an abnormal breast exam or mammogram. Participants were approached by study staff during their initial surgical consult and asked to complete two short series of questionnaires and to provide blood samples for biological analyses. Pre-biopsy questionnaires were completed following initial surgical consult for breast biopsy. Post-biopsy questionnaires were completed after participants obtained results of their breast biopsy. Participants had the option to complete questionnaires either in the consult office within the cancer center or via a web-based survey from home if preferred. Biopsy results were retrospectively determined at the time of data consolidation from participants' pathology reports and charts.

Measures

Pittsburgh Sleep Quality Index (PSQI). The Pittsburgh Sleep Quality Index (PSQI; Buysse, Reynolds, Monk, Berman, & Kupfer, 1989) is a standardized self-report measure of sleep quality designed to determine patterns of sleep dysfunction through

assessment of both qualitative and quantitative data and also to allow for calculation of a single global score to convey quality and severity of overall sleep problems (Carpenter & Andrykowski, 1998). A global PSQI score above 5 is considered as an indication of significant sleep disturbance (Buysse, Reynolds, Monk, Berman, & Kupfer, 2000). The PSQI consists of 19 items that, taken together, produce a single global sleep quality index as well as seven component scores aimed at representing standard areas most commonly assessed by clinicians. These component scores reflect sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance, use of sleep medications, and daytime dysfunction. The PSQI also collects information about typical bed time, wake time, number of actual hours slept, and number of minutes to fall asleep. The other fifteen PSQI items are forced-choice Likert-type scales. Higher scores on the global index as well as the seven component scales represent poorer sleep quality. The psychometric properties of the PSQI were originally supported with data collected from a sample of 52 healthy subjects and 96 individuals with a history of sleep problems (Buysse et al., 1989). Since that time, the PSQI has been utilized in a variety of populations, including healthy individuals of varying ages (Hoch, Dew, Reynolds, & Monk, 1994), trauma survivors (Mellman, Kulick-Bell, Hebding, & Nolan, 1995), and patients with mood disorders, panic disorders, social phobia, and breast cancer patients (Nierenberg, Adler, Peselow, Zornberg, & Rosenthal, 1994; Pasternak, Reynolds, & Houck, 1994; Reynolds, Hoch, & Buysse, 1993; Stein, Chartier, & Walker, 1993). The PSQI has demonstrated internal consistency, convergent and discriminant construct validity, and consistent Chronbach's alphas across multiple samples (Carpenter & Andrykowski, 1998).

Positive and Negative Affect Schedules (PANAS). The Positive and Negative Affect Schedule (PANAS; Watson et al.,1988) is a 20-item self-report measure that consists of two 10-item mood scales which represent positive and negative affect respectively. The PANAS was developed using a sample of undergraduate students but has since been validated with a wide variety of adult populations. Each of the 20 items is rated on a 5-point forced-choice Likert-type scale ranging from 1 (very slightly or not at all) to 5 (extremely) the indicate the degree to which the participant endorses a particular feeling state within a specified time frame. Scores for each affect scale range from 10-50, with higher scores representing higher levels of negative or positive affect. Results of a recent study with a large, non-clinical sample of 1,003 members of the general adult population provided normative data for both positive (mean = 31.31, SD = 7.65) and negative (mean = 16, SD = 5.9) affect scales (Crawford & Henry, 2004). Time frame for the PANAS can be adjusted to reflect positive and negative affect for any range from in the present moment to over the course of the last year. Watson, Clark, and Lee (1998) have demonstrated alpha coefficients for various time reference periods ranging from .84 to .90. Both subscales of the PANAS have also been shown to demonstrate discriminant and convergent validity with other established measures. The two scales have been shown to be highly internally consistent and stable (Watson, 1988).

Interleukin-6 (IL-6) and C-Reactive Protein (CRP). Blood samples were collected from participants via inner elbow venipuncture and collected into vacutainer tubes. Samples were prepared via centerfuge and serum was collected and subsequently frozen at negative eighty degrees celcius. Serum was then analyzed for levels of IL-6 and CRP using Luminex Multiplex Bead assays according to manufacturer's instructions.

Data Analyses. To ensure a normal distribution of scores, values above or below three standard deviations of the mean for CRP and IL-6 were removed for further analyses. Square root and natural log transformations were then conducted for CRP and IL-6, respectively. Non-detectable levels of IL-6 were designated as zero values for subsequent analyses.

All data analyses were performed using SPSS version 17.0 (SPSS, Inc., 2009). We first conducted exploratory data analyses to assess demographic composition of the sample. Bivariate correlation matrices were then computed in order to determine associations between self-report measures (PSQI and PANAS) and biological markers (CRP and IL-6), and between these variables and potential covariates. Potential covariates included age of participants, time interval between pre- and post-biopsy time points, as well as several self-report questionnaire measures. Self-report measures included the Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1982), which detects states of depression and anxiety in medical patients; the European Organization for Research and Treatment of Cancer quality of life questionnaire (EORTC; Aaronson et al., 1993), which assesses quality of life in cancer patients; and the Brief Fatigue Inventory (BFI; Mendoza et al., 1999), which assesses fatigue in clinical settings. The data were then spit into subgroups based on cancer diagnosis and correlational analyses were repeated. Partial correlation matrices were then computed in order to allow for determination of associations between all study measures with covariates included. General linear model repeated measures tests were conducted to examine change in study measures over time with cancer diagnosis as a between subjects

variable. Finally, residualized change scores were computed to further examine relationships between study measures over time.

Results

Participant Characteristics. Relevant demographic information for the total study sample as a whole and sub-grouped by diagnostic status is detailed in Table I. Although complete questionnaire and biological data were obtained for a total of 47 participants, limited demographic data were available. The average age of participants was 53-years-old (SD = 10.67). The interval of time between completion of the two sets of study questionnaires varied with a mean time to completion of 25.5 days (SD = 26). The study sample was comprised predominantly of Caucasian women (51.1%) with small numbers of African-American (4.3%) and Hispanic (6.4%) also included. Information regarding ethnicity was not available for 18 of 47 participants. All participants underwent surgical breast biopsy over the course of their participation in the present study, with 32 (68.1%) women receiving a benign diagnosis and 15 (31.9%) diagnosed with breast cancer.

Descriptive Statistics for Study Measures. Descriptive characteristics for all study scales and biological markers are detailed in Tables IIa and IIb. The average detected serum concentration of CRP at the pre-biopsy time point was 7,248.06 mg/dL (SD = 7,823.91) and at post-biopsy was 8,358.26 mg/dL (SD = 8,597.71). Mean detected IL-6 at the pre-biopsy time point was 252.168 pg/mL (SD = 545.15) and at post-biopsy was 245.86 pg/mL (SD = 518.55). At the pre-biopsy time point, average score on the PANAS positive affect (PA) subscale was 25.1 (SD = 6.1), which is within normal range for this

scale. Post-biopsy average negative affect (NA) score was 29.79 (SD = 6.34). This score is more than two standard deviations above the mean score for normative samples. At the post-biopsy time point, average PA was 23.75 (SD = 6.51), which is within normal range. Post-biopsy average NA score was 29.32 (SD = 7.44), which is also more than two standard deviations above the normative mean score. Average global PSQI index score at pre-biopsy was 7.27 (SD = 3.31) and post-biopsy average score was 7.02 (SD = 3.59). The majority of participants demonstrated significant sleep disturbance (average score above 5) at both the pre- and post- biopsy time points, regardless of cancer status.

Associations between PSQI, PANAS and Biological Markers. Correlation coefficients were calculated to explore potential associations between study measures and potential covariates. Partial correlation coefficients were then calculated to explore these associations while statistically controlling for anxiety (HADSA), depression (HADSD), well-being (EORTC), and fatigue (BFI) at baseline. Results are detailed in Table III.

Transformed CRP at both pre- and post-biopsy time points was positively associated with post-biopsy PSQI scores ($\underline{r}$ = .384, $\underline{p}$<.05; $\underline{r}$ = .375, $\underline{p}$<.05). Transformed IL-6 was not associated with any other study measure. Both positive and negative affect at the pre-biopsy time point were associated with positive ($\underline{r}$ = .798, $\underline{p}$<.01) and negative ($\underline{r}$ = .917, $\underline{p}$<.01) affect post-biopsy. The PANAS positive affect subscale was also shown to be positively associated with the negative affect subscale at both pre-biopsy ($\underline{r}$ = .492, $\underline{p}$<.05) and post-biopsy ($\underline{r}$ = .459, $\underline{p}$<.05) time points.

Data were then split into two subgroups based upon diagnostic status and partial correlation coefficients were once again computed. For participants with a benign breast

cancer diagnosis, post-biopsy transformed CRP was associated with post-biopsy PSQI (r = .482, p = .05) but not with pre-biopsy PSQI, although that relationship did approach significance (r = .429, p = .086). For participants with a positive diagnosis of breast cancer, pre-biopsy transformed CRP was associated with pre-biopsy negative affect (r = .758, p<.05). No associations between IL-6 and other measures were found for either group. No associations were found between PSQI and other measures. Pre-biopsy positive affect for participants with a benign diagnosis was shown to be related to post-biopsy positive affect (r = .795, p<.01) and to post-biopsy negative affect (r = .851, p<.01) and time two (r = .753, p<.01). Pre-biopsy negative affect for these participants was associated with post-biopsy negative affect (r = .680, p<.01) and to post-biopsy positive affect (r = .769, p<.01). For participants with a positive cancer diagnosis, pre-biopsy positive affect was associated with pre-biopsy negative affect (r = .824, p<.05) but not with positive or negative affect post-biopsy. Pre-biopsy negative affect for this group was associated with post-biopsy negative affect (r = .459, p<.05) and post-biopsy positive affect was associated with post-biopsy negative affect (r = .898, p<.05).

PSQI Component Scales. General linear model repeated measures analyses were conducted to explore potential main effects (cancer status and time point) as well as interaction effects (cancer status x time point) for PSQI component scales. For all PSQI component scales, a higher score indicates increased impairment. For all analyses, time interval between pre- and post-biopsy time points was entered as a covariate. Results are depicted in Figures 1-3. For the PSQI component score reflecting sleep latency, a significant interaction effect was found between time point and cancer status (F(1, 33) = 4.725, p<.05), indicating a pre- to post-biopsy improvement in sleep latency scores for

participants diagnosed with breast cancer relative to those with a benign diagnosis. No significant main effects were demonstrated for diagnostic status or for time point. A similar result was shown for the PSQI component score representing daytime dysfunction, with a significant interaction effect between time point and cancer status ($F(1, 33) = 7.008$, $p<.05$), indicating a pre- to post-biopsy improvement in daytime dysfunction scores for participants diagnosed with breast cancer relative to those with a benign diagnosis. No significant main effects were found for cancer diagnostic status or for time point.

Group Differences in Immune Response Markers and Affect. General linear model repeated measures analyses were also conducted to explore potential main effects (cancer status and time point) as well as interaction effects (cancer status x time point) for PSQI global scores, PANAS positive and negative affect scales, CRP and IL-6. No significant main effects or interaction effects were found for PSQI, PANAS positive and negative affect scales, or IL-6. However, a significant main effect was found for CRP ($F(1, 41) = 4.241$, $p<.05$), indicating an increase in transformed CRP from pre- to post-biopsy regardless of cancer diagnosis (see Figure 4). No significant main effect for cancer status or significant interaction between cancer status and time point was found. Results are detailed in Figure 4.

In order to further examine relationships between study scales and immune markers, residualized change scores were computed for PANAS positive and negative affect scales, PSQI global scores, transformed CRP and transformed IL-6. Delta scores for each of these variables were created and entered into stepwise linear regression analyses. Post-biopsy values served as dependant variables. Covariates were entered as

level-one independent variables, pre-biopsy values were entered as level-two independent variables, and delta scores were entered as level-three independent variables. Following initial analyses, data were split into subgroups by diagnostic status and residualized change scores were calculated once again.

Initial analyses conduced with the total sample did not indicate that any of the independent variables accounted for a significant change in level of CRP over time. However, when the data were split by cancer diagnosis, results indicated that for women who received a benign diagnosis, scores on the PANAS positive affect scale increased with levels of CRP ($F(1,18) = 7.728$, $p < .05$, $\beta = .279$). A trend toward significant was also noted for change in PANAS negative affect scores occurring with increased level of serum CRP in the benign group ($F(1,18) = 3.022$, $p = .99$, $\beta = .194$). A similar finding was also noted when PANAS positive affect score was entered as the dependent variable for the total study sample, with increased positive affect increasing as serum CRP increased ($F(1,41) = 8.168$, $p < .01$, $\beta = .276$). A significant relationship was also indicated between increases in positive and negative affect over time for the total sample ($F(1,43) = 9.125$, $p < .01$, $\beta = .299$). When data were broken into subgroups by diagnostic status, no significant relationships were noted between positive affect and other variables for women diagnosed with breast cancer. For the benign group, however, the relationship between positive and negative affect persisted ($F(1,20) = 6.489$, $p < .05$, $\beta = .260$). When PANAS negative affect score was entered as the dependent variable for the total sample, a significant relationship between positive and negative affect was indicated once again ($F(1,40) = 6.245$, $p < .05$, $\beta = .247$). No significant residualized change scores were noted

for negative affect when data were split by diagnosis. No significant residualized change scores were noted when IL-6 or PSQI index score were entered as a dependent variables.

Discussion

The overarching purpose of the present study was to further investigate the impact of breast cancer screening on previously unstudied or understudied aspects of psychological and physiological health, including sleep quality, negative and positive affect, and biomarkers of immune system response. This study further aimed to explore between-group differences in serum cytokine levels, sleep quality, and affect based on diagnostic status over the course of time between surgical consult and diagnosis following breast biopsy in order to determine whether receipt of a benign diagnosis will significantly reduce level of psychological distress. To this end, measurement of sleep quality, positive and negative affect, and serum cytokines was conducted at two time points, pre- and post- surgical breast biopsy, in a convenience sample of women referred to the Neag Comprehensive Cancer center for evaluation of an abnormal breast mass.

A total of 47 participants completed questionnaire and biological measures at both study time points. Although limited demographic information was available for this sample, participants were primarily women of a typical age for breast cancer screening with an average age of 53-years-old, and were primarily Caucasian. All women underwent a surgical breast biopsy procedure over the course of the study. Of the 47 participants that completed the study, 32 received a benign diagnosis and 15 were diagnosed with breast cancer. These figures are also consistent with percentages reported in large scale studies (deKoning, 2000; Wardle & Pope, 1992).

As the measures included in the present study had not previously been assessed in a similar patient population, we first calculated basic descriptive statistics for the group as a whole, and then by diagnostic subgroup, in order to compare average scores on the PSQI and PANAS scales for our sample with normative data available for these measures. As past research consistently reports elevated levels of psychological distress, we expected that scores on both scales would be significantly elevated relative to normative data (Crawford & Henry, 2004; Watson et al., 1998). Results confirmed our hypotheses. For the sample as a whole as well as for diagnostic sub-groups, mean PSQI global index scores were above the level established by creators of the measure as indicative of significant sleep disturbance (global score >5). This was true at both pre- and post-biopsy time points. We next examined the PANAS subscales reflecting negative and positive affect. As no cut-off scores have been established for this measure, we used as a comparison sample data from a large (1,003) general population sample of adult men and women (Crawford & Henry, 2004). Results indicated that while positive affect for the total sample and sample subgroups was within normal range at both pre-and post-biopsy time points. Results for the negative affect scale, however, revealed substantial elevations in negative affect (greater than two standard deviations above the normative sample mean) for the total sample and subgroups at both time points. These results not only provide additional evidence of the stressful nature of breast cancer diagnostic testing but also provide an initial indication that sleep and mood state are negatively impacted during the breast cancer diagnostic phase.

Another aim of this study was to examine associations between sleep quality, negative and positive affect, and serum cytokine levels. To serve this purpose, partial

correlation analyses were conducted to evaluate relationships between these study variables. In order to control for potentially confounding factors, anxiety, depression, well-being, and fatigue were statistically controlled for these analyses. As sleep quality, negative and positive affect, and levels of serum cytokines have been shown to be impacted during stressful experiences (e.g. Gram et al., 1990; Pisano, Earp, Schell, Vokaty, & Denham, 1998; Wardle & Pope, 1992), we expected that relationships would emerge between these study variables for our sample. Our hypotheses were partially confirmed by analyses conducted with the total sample. Results indicated that higher levels of serum CRP at both time points were associated with poorer sleep quality at the post-biopsy time points. This finding indicates that women who were experiencing and reporting lower quality of sleep post-biopsy also demonstrated increased levels of this circulating pro-inflammatory cytokine, a biological marker of stress-related immune system activation. However, no such associations were found between IL-6 and the other study scales. Although this finding does not support our hypotheses, it is likely that our failure to detect relationships between IL-6 and the other study scales is due at least in part to the high number of participants with non-detectable levels of IL-6. In order to include these participants' data for analyses, non-detectable levels were entered as zero, which resulted in a negatively skewed distribution, potentially inhibiting our ability to statistically detect associations. As other studies have shown that decreases in IL-6 are associated with the distress experienced by patients undergoing cancer screening (Glaser et al., 2003; Konsman et al., 2002; Reichenberg et al., 2001), it is likely that we would have seen similar results if the variability of our data were not limited.

An additional unexpected finding also emerged from correlational analyses. Results indicated a positive association between positive and negative affect for the total sample at both pre- and post-biopsy time points, suggesting that participants with higher levels of positive affect also demonstrated higher levels of negative affect. This is somewhat unusual as prior literature consistently reports negative correlations between these two scales (Watson, 1998). Although positive and negative affect are now widely considered to reflect distinct constructs, elevated levels of both positive and negative affect are not typically noted in prior research. However, as was previously discussed, the diagnostic phase of breast cancer treatment represents a highly stressful experience that is characterized by anxiety and psychological distress. As high levels of both positive and negative affect represent emotional activation (Watson et al., 1988), it is fitting that elevations across these scales would be exhibited by women undergoing a highly emotionally activating experience. As lower levels of positive affect are typically associated with symptoms of depression (Crawford & Henry, 2004), these results are consistent with prior research that has not found a substantial increase in depression for women undergoing breast biopsy relative to healthy samples (Ekeberg et al., 2001).

Following these group-wide analyses, the sample was divided into subgroups based on cancer diagnosis and analysis of associations between study measures was repeated. Results for the benign group once again indicated an association between serum CRP and sleep quality, with higher CRP related to poorer post-biopsy sleep quality for this group. This relationship was not detected in the breast cancer group. However, it is unclear whether this is truly reflective of a lack of association or to a lack of statistical power due to the limited number of participants in this subgroup. Despite the small

number of participants in the positive diagnosis group, negative affect for this group was related to level of serum CRP, indicating that participants with higher pre-biopsy negative affect also demonstrated higher levels of pre-biopsy serum CRP. This finding is in keeping with study hypotheses that predicted associations between study measures indicating psychological distress and serum cytokine levels. The group-wide relationship between positive and negative affect was also demonstrated by sub-group analyses. For both the benign and positive diagnosis subgroups, participants with higher levels of negative affect also demonstrated higher levels of positive affect at both pre-and post-biopsy time points. If the association between high positive and negative affect is reflective of a broad emotional activation resulting from an acutely stressful experience, than these results might be taken as support for the assumption that breast cancer screening is associated with acute emotional activation even for women who receive a benign diagnosis.

To further examine the relationship between changes in PSQI, PANAS scales, and cytokine levels over time, residualized change score analyses were conducted. Results of these analyses further supported the presence of high levels of both positive and negative affect across diagnostic subgroups. Not only was increased positive affect predictive of increases in serum CRP for women who received a benign diagnosis, but increases in positive affect were predictive of increases in negative affect both for the group as a whole and within each diagnostic subgroup.

Another aim of the present study was to determine whether participants would demonstrate a differential pattern of impairment in terms of sleep quality, affect, and serum cytokine levels depending on their diagnostic status. As a positive breast cancer

diagnosis is sometimes a traumatic experience, we expected that impairments in the positive diagnosis subgroup would remain stable or increase from pre- to post-biopsy while scores for the benign group would indicate improvement in terms of sleep and affect, along with a corresponding decrease in serum cytokines, after biopsy results were received. These hypotheses were not confirmed. Results indicated neither improvements in sleep quality or affect nor decreased levels of serum cytokines were noted in women who received a benign diagnosis. Conversely, results for several scales indicated improved sleep quality for women diagnosed with breast cancer relative to women who received a benign diagnosis. Results of repeated measures analysis that compared PSQI component scores for benign and positive diagnosis subgroups across time points indicated that women with a positive diagnosis demonstrated improved levels of sleep latency and daytime dysfunction relative to those with a benign diagnosis from pre- to post-biopsy. In other words, women who were diagnosed with breast cancer showed improvements in the time it took to fall asleep and felt more rested after receiving their diagnosis relative to women who received a benign diagnosis.

Although these results were contrary to our hypotheses, they do provide further support for the argument that it is the experience of uncertainty that leads to the acute psychological distress consistently shown in women undergoing breast cancer screening and breast biopsy. As was previously noted, uncertainty in illness occurs when an individual is made aware of the possibility that they might have a life-threatening disease without being able to immediately confirm positive or negative diagnosis (Jordens, Little, Paul, & Sayers, 2001). Exposure to the period of uncertainty between detection of an abnormal breast mass and definitive breast cancer diagnosis has been shown to impact

both the beliefs and the behaviors of women who receive a benign diagnosis. Studies have shown that women who have received a benign diagnosis following breast biopsy are less likely to comply with future recommended screening procedures (e.g. Andrykowski et al., 2002; Barton et al., 2004). Increase breast cancer specific worry has also been shown in women who have received a benign breast biopsy as has heightened perceived 10-year and lifetime risks for eventual positive breast cancer diagnosis (Andrykowski et al., 2002). Overall, evidence suggests that it is the experience of uncertainty that is causing the acute distress experienced by women undergoing breast biopsy. If this is the case, then it is possible that receipt of a benign diagnosis serves to perpetuate feelings of uncertainty as women who receive such a diagnosis believe that they are at an increase risk for developing breast cancer in the future. While receipt of a positive diagnosis is a frightening and traumatic experience, it also represents a resolution of uncertainty. Under these circumstances, the results of the present study might indicate that women with a benign diagnosis fail to demonstrate improvements in sleep quality and affect because they continue to experience uncertainty around their long-term physical health.

Results also indicated that both groups showed an increase in serum CRP from pre-to post biopsy time points regardless of the diagnosis that they received. This finding provides further support for the impact of the acute stress experienced during breast cancer diagnostic testing on levels of this circulating pro-inflammatory cytokine. No additional findings emerged in terms of levels of serum IL-6 or in terms of negative and positive affect scales.

Limitations and Future Directions. Several limitations were apparent in the present study. The primary limitation of this study was the size and diversity of the study sample, which primarily consisted of Caucasian women 50 years or older. We were also limited in terms of demographic information regarding socioeconomic status, medical history, and family history of breast cancer diagnosis. Due to the small number of participants overall and especially within the positive diagnosis group, it is possible that analyses were impacted by Type II error. However, the measures included in the present study are novel and the results that were evidenced provide important direction for future research.

In order to continue to examine the role of uncertainty in the psychological distress demonstrated during breast cancer screening and diagnosis, future research should involve long-term research with larger and more diverse samples that would specifically examine this construct to determine how uncertainty impacts symptoms of psychological distress over time for women with benign breast biopsy. If future research bears out the theory that uncertainty, along with associated psychological distress, persists beyond receipt of definitive diagnosis for women with benign breast biopsy, than this might be a fertile area for potential intervention.

Summary. Overall, results of the present study provide additional evidence for the negative psychological and physiological impact of breast cancer screening and diagnosis. As sleep quality and positive and negative affect had not previously been examined within this population, the present study represents the first exploration of the impact of breast cancer screening on these important constructs. Results indicated substantial elevations in terms of poor sleep quality and negative affect in this group

relative to normative samples as well as improved sleep latency and daytime dysfunction in the positive versus benign diagnosis group. In keeping with prior research, results indicated increased levels of a biomarker of inflammation from pre-to post-biopsy time points. Results also indicated a positive association between positive and negative affect for this sample, and positive and negative affect were shown to be predictive of each other from pre- to post-biopsy time points both for the group as a whole and for diagnostic subgroups. These findings might provide initial support for the presence of broadly heightened emotionality occurring in women undergoing breast cancer diagnostic testing and might also provide an explanation for inconsistencies in prior research around the presence of depression symptoms in this population. Finally, results of the present study provide some additional support for the importance of uncertainty in producing the acute psychological distress consistently reported in women undergoing breast cancer screening and breast biopsy.

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Appendices

TABLE I
Demographic Information – Means and Frequencies

	Total	Positive Diagnosis	Benign Diagnosis
Age Mean Scores (SD)	52.93(10.67)	56.6(8.93)	51.22(11.11)
Time 1 – Time 2 Interval mean scores (SD)	25.5(26)	17.3(9.91)	29.58(30.61)
Ethnicity			
Black, Non-Hispanic	4.3%	0%	6.3%
Hispanic	6.4%	6.7%	6.3%
White, Non-Hispanic	51.1%	53.3%	50%
Not Reported	38.3%	40%	37.5%

TABLE IIa
Descriptive Statistics, Mean Scores (SD) – Pre-biopsy

	Total	Positive Diagnosis	Benign Diagnosis
PSQI Index Score	7.28(3.5)	7.27(2.71)	7.28(3.86)
PANAS Positive Affect	25.11(6.1)	25.2(5.11)	23.81(6.07)
PANAS Negative Affect	29.79(6.34)	30.1(5.65)	29.66(6.72)
CRP	5612.32(4690.1)	4611.43(3918.59)	6079.4(5002.35)
IL-6	133.7(248.87)	109.8(234.16)	144.82(258.55)

TABLE IIb
Descriptive Statistics, Mean Scores (SD) – Post-biopsy

	Total	Positive Diagnosis	Benign Diagnosis
PSQI Index Score	7.02(3.59)	6.86(3.84)	7.09(3.54)
PANAS Positive Affect	23.74(6.51)	23.6(7.59)	29.81(6.07)
PANAS Negative Affect	29.32(7.44)	27.53(9.0)	30.16 (6.58)
CRP	7048.24(5852.36)	7238.64(6561.77)	6962.2(5617.03)
IL-6	130.69(238.04)	103.85(230.59)	143.22(244.28)

Table III
Partial Correlations for PSQI, PANAS, CRP and IL-6

Scale	PSQI T1	PSQI T2	Panas Pos T1	Panas Pos T2	Panas Neg T1	Panas Neg T2
PSQI						
Total T1	-	.551*	.078	-.105	-.008	-.225
Total T2	.551*	-	.032	-.222	.186	-.168
Benign T1	-	.516*	.075	.193	-.05	.028
Benign T2	.516*	-	-.106	.145	.057	.087
Positive T1	-	.566*	-.204	-.105	-.008	-.225
Positive T2	.566*	-	-.395	-.222	.186	-.168
PANAS Pos						
Total T1	.078	.032	-	.492	.798*	.466*
Total T2	-.105	-.222	.492*	-	.399*	.917*
Benign T1	.075	-.106	-	.795*	.851*	.753*
Benign T2	.193	.145	.795*	-	.769*	.917*
Positive T1	-.204	-.395	-	.492*	.798*	.466*
Positive T2	-.376	-.422	.647	-	.399*	.917*
PANAS Neg						
Total T1	-.008	.186	.798*	.399*	-	.459*
Total T2	-.225	-.168	.466*	.917*	.459*	-
Benign T1	-.05	.057	.851*	.769*	-	.680*
Benign T2	.028	.087	.753*	.917*	.680*	-
Positive T1	.132	.103	.824*	.798*	-	.459*
Positive T2	-.352	-.107	.712†	.466*	.459*	-
CRP						
Total T1	.338†	.384*	.049	-.060	.225	-.079
Total T2	.271	.375*	-.138	-.160	.043	-.146
Benign T1	.372	.407	-.083	.123	-.058	-.028
Benign T2	.429†	.482*	-.191	.137	-.104	.044
Positive T1	.419	.687†	.049	.049	.225	-.079
Positive T2	.008	.567	-.138	-.138	.043	-.146
IL-6						
Total T1	.256	.128	.128	.233	.027	.253
Total T2	.258	.063	.063	.195	-.021	.214
Benign T1	.405	.270	.219	.219	.024	.197
Benign T2	.393	.254	.193	.193	.013	.195
Positive T1	.419	.397	.128	.128	.027	.253
Positive T2	.987	.624	.063	.063	-.021	.214

* p >.05 † p< .10

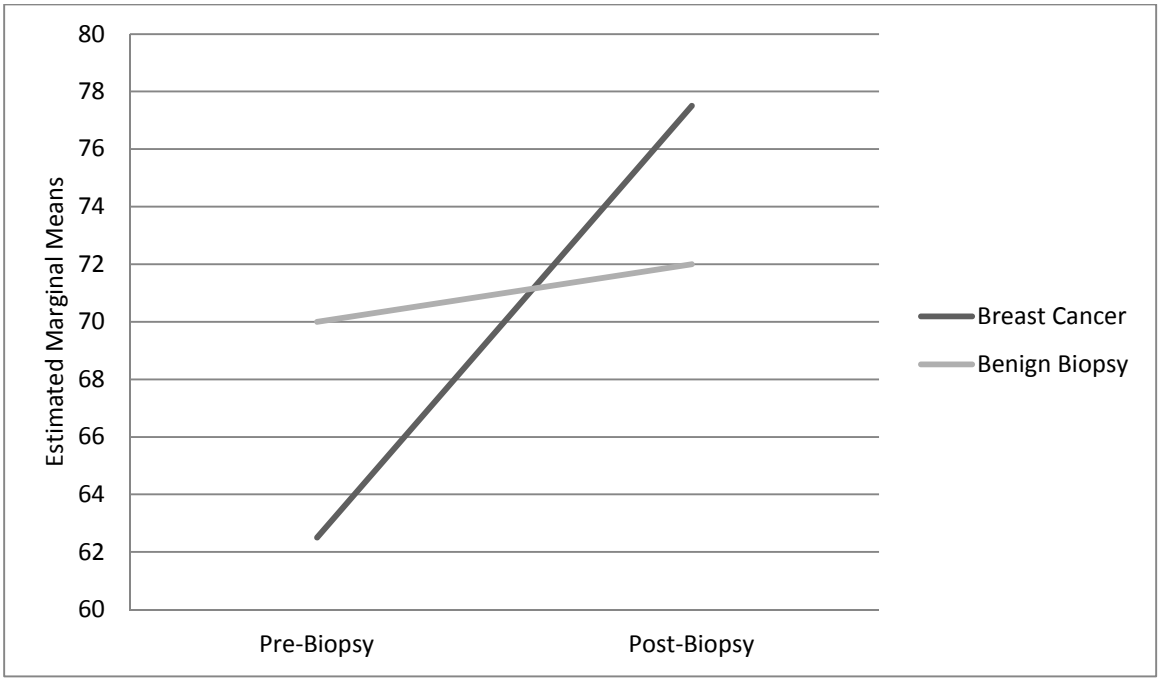

Figure A. Pre- to Post-biopsy changes in CRP by diagnostic subgroup.

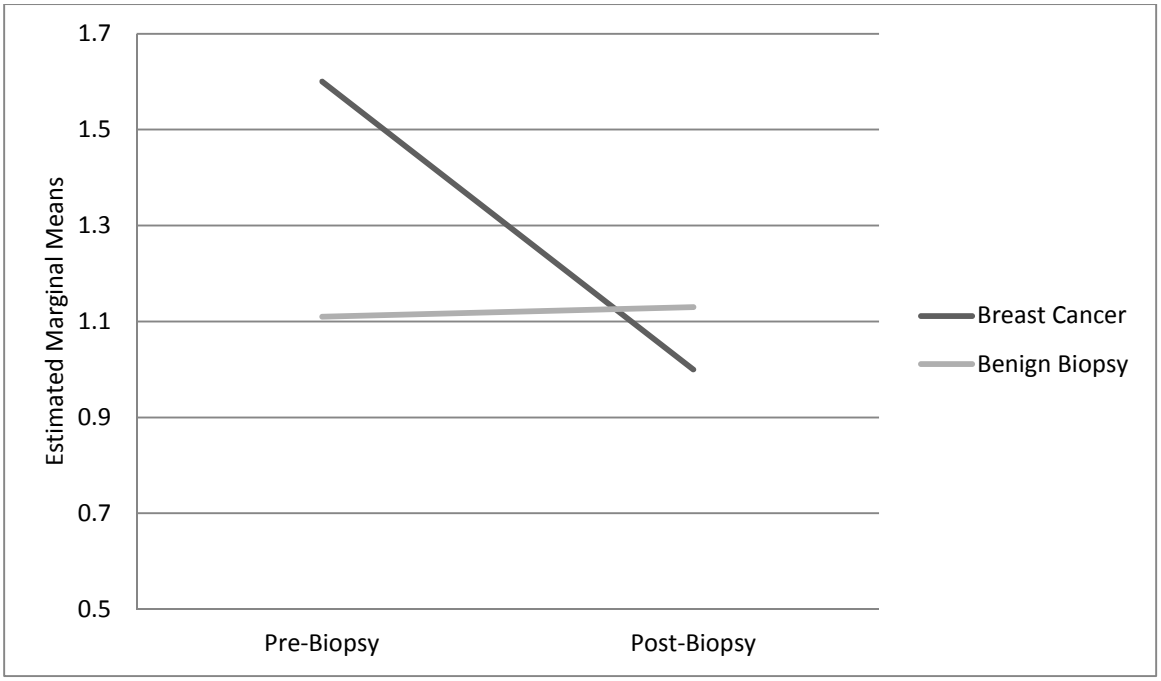

Figure B. Pre- to post-biopsy changes in Pittsburgh Sleep Quality Index Sleep Latency component scores by diagnostic subgroup.

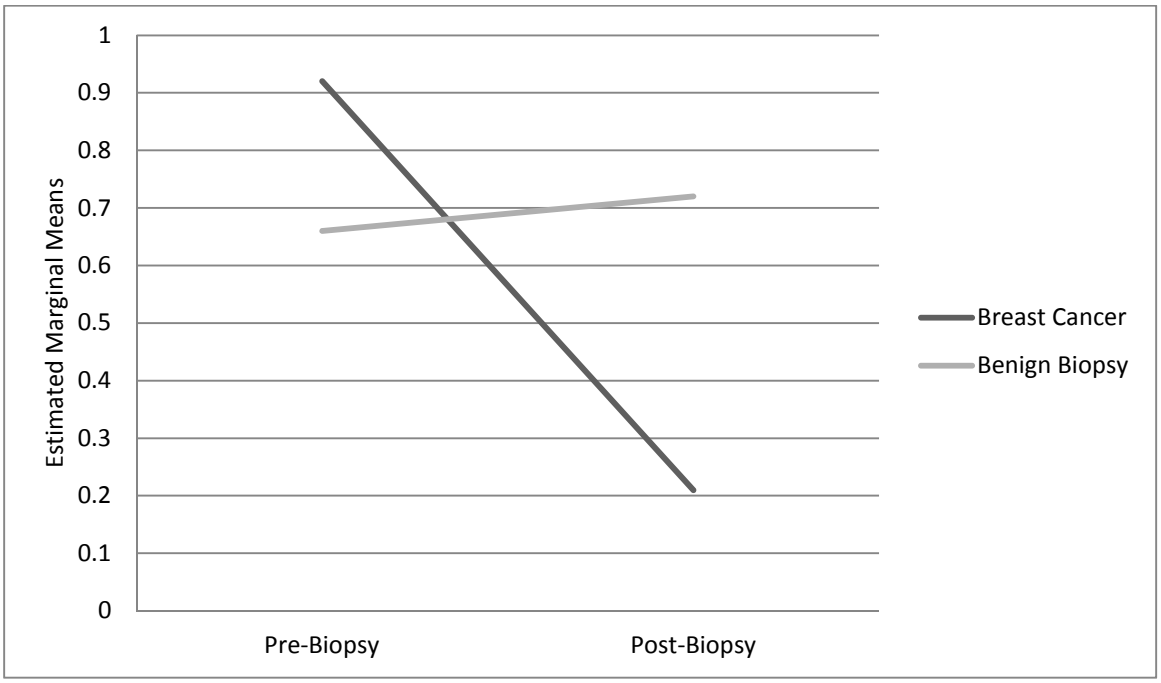

Figure B. Pre- to post-biopsy changes in Pittsburgh Sleep Quality Index Daytime Dysfunction component scores by diagnostic subgroup.

Appendix: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC) *

* The EORTC QLQ-C30 is a copyrighted instrument. It is currently available in the following languages: Danish, Dutch, French, German, Italian, Japanese, Norwegian, and Swedish. Requests for permission to use the instrument and for scoring instructions should be sent either to Neil K. Aaronson, Ph.D., The Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands, or to Ann Cull, Ph.D., Secretary, EORTC Study Group on Quality of Life, Department of Clinical Psychology, Outpatient Clinic E, Western General Hospital, Crewe Road, Edinburgh EH4 2XU, United Kingdom.

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:

Your birthdate (Day, Month, Year):

Today's date (Day, Month, Year):

	No	**Yes**
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2
2. Do you have any trouble taking a long walk?	1	2
3. Do you have any trouble taking a short walk outside of the house?	1	2
4. Do you have to stay in a bed or a chair for most of the day?	1	2
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2
6. Are you limited in any way in doing either		

your work or doing household jobs?	1	2
7. Are you completely unable to work at a job or to do household jobs?	1	2

DURING THE PAST WEEK:

	Not at All	**A Little**	**Quite a Bit**	**Very Much**
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering				

things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

FOR THE FOLLOWING QUESTIONS PLEASE CIRCLE THE NUMBER BETWEEN 1 AND 7 THAT BEST APPLIES TO YOU

29. How would you rate your overall physical condition during the past week?

1	**2**	**3**	**4**	**5**	**6**	**7**
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	**2**	**3**	**4**	**5**	**6**	**7**

Very
poor Excellent

Appendix: Hospital Anxiety and Depression Scale (HADS)

Hospital Anxiety and Depression Scale (HADS)

Patients are asked to choose one response from the four given for each interview. They should give an immediate response and be dissuaded from thinking too long about their answers. The questions relating to anxiety are marked "A", and to depression "D". The score for each answer is given in the right column. Instruct the patient to answer how it currently describes their feelings.

A	**I feel tense or 'wound up':**	
	Most of the time	3
	A lot of the time	2
	From time to time, occasionally	1
	Not at all	0

D	**I still enjoy the things I used to enjoy:**	
	Definitely as much	0
	Not quite so much	1
	Only a little	2

	Hardly at all	3

A	**I get a sort of frightened feeling as if something awful is about to happen:**	
	Very definitely and quite badly	3
	Yes, but not too badly	2
	A little, but it doesn't worry me	1
	Not at all	0

D	**I can laugh and see the funny side of things:**	
	As much as I always could	0
	Not quite so much now	1
	Definitely not so much now	2
	Not at all	3

A	**Worrying thoughts go through my mind:**	
	A great deal of the time	3
	A lot of the time	2
	From time to time, but not too often	1
	Only occasionally	0

D	**I feel cheerful:**	
	Not at all	3
	Not often	2
	Sometimes	1
	Most of the time	0

A	**I can sit at ease and feel relaxed:**	
	Definitely	0
	Usually	1
	Not Often	2

	Not at all	3

D	**I feel as if I am slowed down:**	
	Nearly all the time	3
	Very often	2
	Sometimes	1
	Not at all	0

A	**I get a sort of frightened feeling like 'butterflies' in the stomach:**	
	Not at all	0
	Occasionally	1
	Quite Often	2
	Very Often	3

D	**I have lost interest in my appearance:**	
	Definitely	3

	I don't take as much care as I should	2
	I may not take quite as much care	1
	I take just as much care as ever	0

A	**I feel restless as I have to be on the move:**	
	Very much indeed	3
	Quite a lot	2
	Not very much	1
	Not at all	0

D	**I look forward with enjoyment to things:**	
	As much as I ever did	0
	Rather less than I used to	1
	Definitely less than I used to	2

	Hardly at all	3

A	**I get sudden feelings of panic:**	
	Very often indeed	3
	Quite often	2
	Not very often	1
	Not at all	0

D	**I can enjoy a good book or radio or TV program:**	
	Often	0
	Sometimes	1
	Not often	2
	Very seldom	3

	Scoring (add the As = Anxiety. Add the Ds = Depression). The norms below will give you an idea of the level of Anxiety and	

	Depression.	
	0-7 = Normal	
	8-10 = Borderline abnormal	
	11-21 = Abnormal	

Reference:

Zigmond and Snaith (1983)

Appendix: Positive and Negative Affect Schedules (PANAS)

PANAS

This scale consists of a number of words that describe different feelings and emotions. Read each item and then circle the appropriate answer next to that word. Indicate to what extent you have felt this way **during the past week**.

1 = Very slightly or not at all	**2 = A little**	**3 = Moderately**	**4 = Quite a bit**	**5 = Extremely**
1. Interested	**1**	**2**	**3**	**4**	**5**
2. Distressed	**1**	**2**	**3**	**4**	**5**
3. Excited	**1**	**2**	**3**	**4**	**5**
4. Upset	**1**	**2**	**3**	**4**	**5**

5.Strong	**1**	**2**	**3**	**4**	**5**
6.Guilty	**1**	**2**	**3**	**4**	**5**
7.Scared	**1**	**2**	**3**	**4**	**5**
8.Hostile	**1**	**2**	**3**	**4**	**5**
9.Enthusiastic	**1**	**2**	**3**	**4**	**5**
10. Proud	**1**	**2**	**3**	**4**	**5**
11. Irritable	**1**	**2**	**3**	**4**	**5**
12. Alert	**1**	**2**	**3**	**4**	**5**
13. Ashamed	**1**	**2**	**3**	**4**	**5**
14. Inspired	**1**	**2**	**3**	**4**	**5**
15. Nervous	**1**	**2**	**3**	**4**	**5**
16. Determined	**1**	**2**	**3**	**4**	**5**
17. Attentive	**1**	**2**	**3**	**4**	**5**
18. Jittery	**1**	**2**	**3**	**4**	**5**
19. Active	**1**	**2**	**3**	**4**	**5**
20. Afraid	**1**	**2**	**3**	**4**	**5**