Stress, Coping, and Immune Function in Breast Cancer

Linda J. Luecken, Ph.D.
Arizona State University

Bruce E. Compas, Ph.D.
The University of Vermont

ABSTRACT

Research has found suggestive links between emotional distress and immune and neuroendocrine measures in cancer patients. Furthermore, several studies have reported that participation in psychological support groups is associated with better health outcomes for cancer patients. However, controversy exists surrounding these findings, and the mechanisms behind such effects are unclear. This article integrates current evidence from several lines of research concerning the relations among coping, psychological adjustment, cortisol and immune function, and disease progression in breast cancer patients. A biopsychosocial model is evaluated in which coping and psychological adjustment are associated with alterations in cortisol levels, immune function, and potential long-term medical outcomes in breast cancer patients. Although strong evidence suggests that coping and psychosocial intervention can improve psychological outcomes for breast cancer patients, potential effects on physiological outcomes remain speculative.

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INTRODUCTION

Breast cancer affects approximately 185,000 women in the United States annually, and an estimated 46,000 women die from the disease each year (1). Four lines of research indicate that a diagnosis of breast cancer can have significant short- and long-term psychological consequences, which may be relevant to disease-related physiological processes. First, from the initial diagnosis through surgery and adjuvant treatment, breast cancer can be a highly stressful experience (2), placing women at high risk of emotional distress. Both voluntary coping responses and involuntary cognitive responses significantly influence the magnitude and course of emotional distress (e.g., 3,4). Second, accumulating evidence suggests that high levels of stress and emotional distress are associated with impairments in hormonal and immune function (5,6). Third, these physiological changes may have important consequences for breast cancer, leading behavioral researchers to suggest that psychological and behavioral factors that influence immune functioning may also influence cancer outcomes (7–9). Fourth, psychosocial interventions with cancer patients have been developed to reduce emotional distress, and that may also result in physiological benefits (10,11).

Reprint Address: L. J. Luecken, Ph.D., Department of Psychology, Box 871104, Arizona State University, Tempe, AZ 85287. E-mail: Linda.Luecken@asu.edu

Several authors have proposed conceptual models linking stress and emotional states with neuroendocrine and immune function in cancer and, ultimately, with cancer prognosis (e.g., 7,12,13); however, controversy exists surrounding the supportive evidence for each step in such a model. In this article we briefly review and integrate evidence from these four lines of research and evaluate theoretical pathways linking psychological factors with physiological outcomes for women with breast cancer. We propose that women's coping and self-regulatory responses play a pivotal role in long-term psychological adjustment and may potentially influence stress-related physiological processes. Emotional distress is associated with increased output of the stress-related hormone cortisol and with suppression of several indexes of immune function. As we review later, these physiological processes have been linked with key prognostic variables for breast cancer, such as tumor size, nodal status, and metastatic spread; however, it is unclear whether the magnitude of stress-related changes can be sufficient to influence disease course. Finally, psychotherapeutic interventions may result in improvements in coping and emotional adjustment, although physiological benefits remain speculative.

A central theme throughout these four lines of research is the importance of self-regulatory and coping processes in adaptation to breast cancer. Self-regulation in response to breast cancer includes regulation of (a) cognitions, including intrusive thoughts and worries; (b) emotions, including anxiety, anger, and dysphoric moods; (c) physiological arousal; and (d) behavior, including tendencies toward withdrawal or avoidance. In this article we do not directly speak to the effects of behavioral factors, such as compliance or alcohol use, on adjustment to cancer; however, these behaviors are conceptualized as components of coping responses. For example, avoidant coping is associated with low levels of compliance with medical recommendations and increased alcohol and drug use (14).

The human immune system is remarkably complex and has yet to be fully understood. It is beyond the scope of this article to describe all psychosocial and physiological factors involved in immune function relevant to breast cancer. Furthermore, bidirectional relations among psychosocial, hormonal, and immune measures have been described (15). This article focuses on well-established links among psychosocial, hormonal, and immunological factors and on a review of pathways that are relatively accessible to measurement by the behavioral researcher. We briefly review current evidence concerning the relations among involuntary stress responses, coping styles, psychosocial adjustment to breast cancer, and physiological parameters relevant to breast cancer. Finally, an evaluation of the status of a biopsychosocial model of stress, coping, and breast cancer pro-

gression is presented, along with directions for future research in this area.

COPING AND PSYCHOSOCIAL ADJUSTMENT TO BREAST CANCER

Diagnosis and treatment of breast cancer can be a highly stressful and emotionally upsetting experience. Women face uncertainty and fears about the severity and treatment of the cancer. Women newly diagnosed with breast cancer generally face a variety of invasive or debilitating surgical and medical treatments, along with many potentially negative side effects (e.g., nausea, lymphedema, hair loss). Adjuvant treatments can significantly impact a woman's ability to maintain social roles within a household or outside employment. After treatment ends, women face uncertainty about their future and the possibility of recurrence. High stress levels can have negative long-term effects on a woman's self-image and can present a significant challenge to marital and family functioning (16,17).

The stress associated with breast cancer diagnosis and treatment can lead to dysregulation of psychological and biological processes. Women with breast cancer are at high risk for emotional distress (most notably anxiety and depressive symptoms) and decreased quality of life, particularly near the time of diagnosis. Elevated symptoms of anxiety and depression near the time of diagnosis are typically reported in 30% to 40% of patients, a rate that is approximately 3 to 4 times that found in community samples (4). Although for many women with breast cancer the level of distress decreases over time, a subset of women remain highly distressed throughout their treatment and recovery (3,4). Recent reports have documented that symptoms of posttraumatic stress disorder (PTSD) are common, and an estimated 3% to 10% of patients may meet clinical criteria for PTSD (18,19).

The level of risk for emotional distress depends on a variety of factors. Younger and less-educated patients or those with more severe cancer tend to experience more psychological distress, particularly near the time of diagnosis (7,20,21). Among the various personality characteristics that have been studied, dispositional optimism, or the tendency to expect positive outcomes, has been most consistently associated with lower symptoms of anxiety and depression and higher quality of life (3,4). Both voluntary and involuntary (automatic) cognitive responses to stress are also important contributors to psychological outcomes. Women often report high levels of involuntary intrusive thoughts and worries about cancer and efforts to suppress or avoid these thoughts (19). Reporting of involuntary intrusive thoughts is typically highest near the time of diagnosis but, for many women, may persist for months or years following diagnosis and treatment (4,22). The experience of involuntary intrusive thoughts, and efforts to suppress these thoughts, are typically highly distressing for women and indicate relatively poor adjustment to the cancer (4,23,24). The tendency to seek out or monitor threat-relevant cues is also associated with increased intrusive thoughts and emotional distress (25).

Voluntary coping responses to stress are deliberate, controlled strategies used to moderate the impact of the stress. We define *coping* as conscious, volitional efforts to regulate one's cognitive, behavioral, emotional, and physiological responses to stress and the stressful aspects of the environment (26). From this perspective, coping is a subset of the broader category of self-regulatory processes. Within our conceptual model, coping responses are distinguished as involving engagement with or disengagement from the source of stress and one's emotional reactions to the stressor (27). Engagement coping is further distinguished as reflecting efforts directed at primary control (problem solving, emotional regulation, emotion expression), or secondary control (acceptance, positive thinking, cognitive restructuring, distraction). Disengagement coping includes several subtypes as well (e.g., avoidance, wishful thinking, denial) but is not further distinguished based on control motivation.

Coping strategies involving primary control engagement with the stressful aspect of breast cancer or one's emotions have been found to predict better emotional adjustment to breast cancer (4). Conversely, coping strategies involving disengagement from the stressor or one's emotions predict poorer adjustment (4,28,29). Coping responses appear to mediate relations among age, education, disease stage, and psychological adjustment (4). Women with earlier stage breast cancer use more engagement-oriented coping strategies (e.g., active, problem-focused) than women with more advanced cancer (30). Coping style may also be associated with cancer outcomes. Epping-Jordan, Compas, and Howell (31) found that although psychological factors were unrelated to initial prognosis, the use of cognitive and behavioral avoidance coping was found to significantly predict cancer progression at 1-year follow-up. Patients reporting high levels of avoidant coping had higher rates of continued presence of the original cancer, recurrence, or mortality at 1-year follow-up. Similarly, Reynolds and colleagues (32) reported that emotion-focused coping, including expression of emotion, predicted longer survival in breast cancer patients.

NEUROENDOCRINE AND IMMUNE CONSEQUENCES OF DISTRESS

The level of emotional distress of breast cancer patients may have physiological consequences relevant to cancer. Numerous investigations have shown reliable relations among stress, affective states, and hormonal and immune alterations. Although many hormonal systems are involved in responding to stress, the hypothalamic–pituitary–adrenal (HPA) axis in particular has been shown to be a key component of the body's stress response (6). At low levels of stress, the HPA axis acts with a regular normal rhythm, but at higher levels of stress it works to actively regulate the body's complex stress responses. Increased cortisol is generally associated with heightened emotional distress and has been associated in noncancer populations with major depressive disorder (MDD) (5,6), panic disorder with agoraphobia (33), and bipolar mania (34). Increased 24-hr production of cortisol is found in approximately 50% of patients with MDD, although decreased cortisol may be associated with "atypical depression" (6,35).

The potentially inhibitory effects of cortisol on immunity are well documented (36). Variations in cortisol levels, even

within normal ranges, can have a substantial impact on immune functions, including decreased antibody production, decreased numbers of macrophages, monocytes, and T cells, decreased lymphocyte proliferative responses, impaired Il-2 production by T cells, and inhibition of NK cell activation (37–40). The potentially inhibitory effects of stress on immune function, including alterations in both humoral and cellular immune mechanisms, are also well documented in both animal and human studies (36).

A large amount of research has shown that affective states, such as bereavement, depression, and loneliness, are associated with depressed immune function (5). Meta-analytic review of relevant studies by Herbert and Cohen (41) found reliable negative correlations between depression and T helper cell (CD4) counts or the CD4/CD8 (T helper/T-killer-suppressor) ratio. Similarly, meta-analytic reviews found reliable associations among stress, negative affect, and depressed immune function (5,36,42,43). Among the most commonly reported alterations are depressed mitogen proliferation responses of lymphocytes (e.g., 5,44,45) and reduced NK cell cytotoxic activity against tumor cells (e.g., 46–48).

Recently, immunosuppressive effects of emotional distress and high stress levels have been shown in breast cancer patients. Andersen and colleagues (49) evaluated levels of intrusive and avoidant thoughts as a measure of stress levels in women newly diagnosed with Stage I or II breast cancer and found significant associations with NK and T-cell activity. High levels of intrusive thoughts were associated with significant declines in NK cell lysis, response of NK cells to rIFN$_\gamma$, and T-cell mitogen-induced proliferative response. Suppression of the activity of lymphokine-activated killer cells was found in breast cancer patients experiencing current clinically relevant depressive symptoms or high-state anxiety; however, no differences were found in NK lytic activity (50). Fredrikson, Furst, Lekander, Rotstein, and Blomgren (51) found compromised NK cell function in breast cancer patients who exhibited high-trait anxiety. Tjemsland and colleagues (52) found that depression, intrusive anxiety, and anxious preoccupation in women newly diagnosed with Stage I or II breast cancer were inversely correlated with total numbers of lymphocytes, B cells, and T helper cells. However, a fatalistic response to the diagnosis was positively correlated with the number of B cells and NK cells.

Although it is clear that stress and negative affective states can influence neuroendocrine and immune function, not all individuals are equally affected psychologically or physiologically by the same stressful situation, even one as objectively stressful as breast cancer. The coping attempts made by an individual may significantly alter psychological and biological outcomes; however, studies evaluating direct relations among cortisol, immune function, and specific coping styles are sparse. Few studies have directly involved cancer patients, and current evidence for relations between coping styles and physiological alterations relevant to breast cancer must be considered preliminary.

Active coping involves a direct, rational approach toward dealing with a problem, but passive coping involves indirect strategies, such as avoidance, withdrawal, wishful thinking, and waiting passively for problem resolution. In a noncancer population, Manyande and colleagues (53) found that the use of active coping imagery was associated with decreased cortisol before and after surgery. Similarly, Ehlert, Patalla, Kirschbaum, Piedmont, and Hellhammer (54) reported that depressive symptoms were associated with passive coping (e.g., escape, social isolation) and increased salivary cortisol. Active coping has also been associated with improved NK cell activity in HIV–1 seropositive men, but passive coping was associated with lower total lymphocyte and T helper cell counts (55,56) and faster disease progression (57). Futterman and colleagues (58) reported that avoidant coping predicted immune suppression in partners of bone marrow transplant patients. In patients with malignant melanoma, avoidant coping style was associated with impairment in NK cell activity (59). However, little is known concerning coping styles and immune or cortisol function in breast cancer patients. An early study reported enhanced NK activity in breast cancer patients who used a coping style of seeking social support (60). More recently, greater quality of social support has been associated with lower cortisol in women with metastatic breast cancer (61). The use of a confidant to discuss personal problems was found to favorably affect breast cancer survival (62). As we review later, coping skills are a common target for intervention and may be associated with improvements in cortisol and immune function in breast cancer patients postintervention.

INVOLVEMENT OF CORTISOL AND THE IMMUNE SYSTEM IN BREAST CANCER

Although many studies have demonstrated that stress and emotional distress can impact neuroendocrine and immune function, the clinical significance for breast cancer patients of these physiological alterations is not clear. The relation of cortisol and immune function to breast cancer development and progression has been the subject of controversy. Furthermore, it is not clear if the magnitude of physiological alterations associated with stress and emotional distress is sufficient to significantly impact cancer progression. Recent evidence is beginning to more clearly demonstrate the role of cortisol and the immune system in the development and progression of tumors; however, very limited data exist linking psychological adjustment to hormonal and immune alterations sufficient in magnitude to alter the progression of cancer. Inconsistent findings have been reported concerning the effects of stressful life events prior to and following diagnosis on cancer progression (e.g., 12,63,64). In particular, stress in the years preceding a diagnosis appears unlikely to affect cancer risk or mortality (12); however, it is less clear if stress following diagnosis and associated physiological alterations can impact cancer outcomes.

The HPA axis is an important regulator of the immune system, and its potential inhibitory effects on immune functioning may influence the development and progression of cancer. Cortisol also appears capable of directly influencing neoplastic cell growth (40). For example, glucocorticoids alter cell adhesiveness, cell division, and metastatic potential (37,40,65). Breast cancer cells have glucocorticoid receptors and are re-

sponsive to cortisol in vitro, although the direction of response remains controversial. Addition of cortisol to cell cultures in vitro has been shown to enhance (66,67), inhibit (68,69), or either enhance or inhibit growth of breast cancer cells (70). A few studies have reported elevated cortisol in breast cancer patients, with the amount of elevation positively correlated with the severity of the cancer (e.g., 37,71,72). Touitou, Bogdan, Levi, Benavides, and Auzeby (73) found disrupted circadian rhythms of cortisol in breast cancer patients. Circadian patterns were abolished in patients with metastatic disease. Sephton, Sapolsky, Kraemer, and Spiegel (74) reported earlier mortality in metastatic breast cancer patients with disrupted circadian rhythms of cortisol.

Recent research also provides evidence that the immune system plays a role in surveillance against tumor initiation and growth and in controlling metastatic spread. Many researchers have highlighted the important role of NK and LAK immune cells in the development and progression of tumors (e.g., 75–78). NK cells are capable of lysing a wide variety of tumor cells in vitro through the release of cytotoxic factors, and they are thought to be important in the body's defense against the metastasis of tumors (79). The T-cell immune response is also important in the control of tumors. T helper cells are involved in the activation of immune effector cells such as macrophages, NK cells, or B cells. Cytotoxic T cells are also capable of directly recognizing and lysing tumor cells. Tumor-specific T cells have been found in the peripheral blood of cancer patients as well as at the site of the tumor (79). Cytotoxic T cells can recognize mucin epitopes associated with breast cancer cells and may play a role in the defense against breast cancer (80).

Breast cancer patients may have a diminished ability of the immune system to recognize or destroy breast cancer cells. Several studies have reported depressed NK activity in breast cancer patients, and patients with more severe cancer had more depressed NK activity (50,75,81). Patients with positive lymph nodes (indicating more severe cancer) were shown to have decreased NK activity relative to node-negative patients (50,82). Levy, Herberman, Lippman, D'Angelo, and Lee (83) reported a negative correlation between NK activity and tumor size. Conflicting evidence was reported by Wiltschke and colleagues (84), who found *increased* NK activity in breast cancer patients compared with patients with benign disease, and no correlations among NK lytic activity and tumor size, nodal status, or stage. Eremin, Ashby, and Stephens (85) found no decrease in natural cytotoxicity of immune cells in breast cancer patients. Shevde, Narendra, Shinde, and Nadkarni (86) found decreased NK function only in postmenopausal breast cancer patients, and Akimoto and colleagues (87) found impaired NK activity only in patients with Stage III or IV disease.

The function of T lymphocytes may also be altered in breast cancer patients. It has been suggested that breast cancer represents a failure of T cells to adequately proliferate in response to breast cancer tumor cells, thereby limiting the immune system's ability to defend against the cancer cells (88). Decreased T-cell proliferative responses have been reported in breast cancer patients relative to controls, with the amount of depression correlated with severity of cancer (81,86,89,90).

Alterations in immune function have been shown to be predictive of disease outcome in breast cancer patients. T-cell proliferative response has been shown to be predictive of survival in breast cancer (81,83,90–92). Wiltschke and colleagues (90) reported that patients showing an increase in T-cell proliferative response from diagnosis to 12 months remained in remission after 3 years, but patients showing a decrease had progressive disease at follow-up. Hacene and colleagues (92) evaluated the prognostic value of several clinical and immunological variables in breast cancer patients, finding that stage of disease, nodal status, and T-cell response to PHA significantly predicted survival.

Similarly, increased NK activity may be related to favorable prognostic outcome in breast cancer. A negative correlation between NK cytotoxicity and spread of tumor has been reported, with increased NK activity associated with decreased tumor spread in women with breast cancer (93). Levy and colleagues (83) found that higher NK cell activity at 15-month follow-up strongly predicted nonrecurrence of breast cancer. However, higher NK activity at time of diagnosis predicted recurrence of disease. Levy suggested that baseline NK activity may reflect a response to more aggressive disease. Alternatively, patients with better long-term outcomes may have had lower peripheral NK activity because of a concentration of NK cells at the tumor site.

EFFECTS OF PSYCHOSOCIAL INTERVENTION ON EMOTIONAL AND PHYSICAL FACTORS IN CANCER

Many studies have shown psychological benefits of psychosocial interventions for cancer patients, and several have been reported specific to breast cancer populations. In a recent meta-analytic review, Meyer and Mark (94) concluded that there is clear evidence that interventions can have positive effects on emotional adjustment, functional adjustment, and treatment of disease-related symptoms (e.g., pain, nausea, coughing). Other benefits have included reductions in pain and traumatic stress symptoms, improved quality of life, psychological adjustment, coping skills, and daily functioning in cancer patients following participation in support groups, individual psychotherapy, educational interventions, or cognitive–behavioral interventions (2,94–99).

Although several studies have shown beneficial effects of psychological interventions on cortisol and immune function in other illnesses such as HIV/AIDS (e.g., 100,101), effects of intervention on physiological outcomes in breast cancer are less clear. A limited number of studies have suggested that psychological interventions may lower cortisol levels and improve immune function in cancer patients. Davis (102) reported biofeedback training or cognitive therapy was associated with significant decreases in cortisol output in Stage I breast cancer patients. Similarly, a 10-week group intervention consisting of relaxation, stress management, and guided imagery was associated with an increased number of circulating lymphocytes and decreased cortisol levels in Stage I and II breast cancer patients relative to control patients (103). Van der Pompe, Duivenvoorden, Antoni, Visser, and Heijnen (72) reported that a

13-session existential–experiential intervention was associated with decreased cortisol levels and NK cell percentages but only for patients with initially high levels or percentages. A 9-week biofeedback, relaxation, and guided imagery intervention was associated with immune enhancement in breast cancer patients relative to a waiting-list control group (104). A 10-week cognitive-behavioral stress-management group intervention was associated with reduced serum cortisol in women with early stage breast cancer through increased benefit finding (105). In contrast, despite finding improvements in psychological adjustment, Hosaka, Tokuda, Sugiyama, Hirai, and Okuyama (106) failed to find an effect of a 5-week intervention consisting of psychoeducation, social support, relaxation, and problem solving on immune function in Japanese breast cancer patients.

A few studies with cancer patients have shown lower recurrence rates and increased survival time following participation in psychosocial interventions. Spiegel, Bloom, Kraemer, and Gottheil (11) found an 18-month survival time advantage in metastatic breast cancer patients following a stress management and social support intervention. Grossarth-Maticek and Eysenck (107) reported longer survival for breast cancer patients receiving individual psychotherapy; however, this research has been criticized for several methodological flaws, suggesting caution in interpretation (95,108). Fawzy and colleagues (10) reported a significant survival advantage for malignant melanoma patients following participation in a group psychotherapy intervention. In contrast, several large-scale, well-controlled studies have failed to find a significant effect of psychosocial intervention on cancer progression or survival time (99,109–111). Furthermore, no randomized controlled studies with nonmetastatic breast cancer patients have been reported. Therefore, survival benefits of psychosocial intervention with breast cancer patients remain highly speculative, and it has not been clearly demonstrated that psychosocial intervention can alter the progression or severity of cancer.

EVALUATION OF A BIOPSYCHOSOCIAL MODEL

The evidence reviewed in the preceding section synthesizes research on stress, coping, psychological adjustment, and physiological outcomes in breast cancer and suggests that when faced with the diagnosis and treatment of breast cancer, the voluntary coping and involuntary cognitive responses employed will significantly influence psychological adjustment. Women who do not cope adaptively and display high levels of involuntary negative stress responses will demonstrate higher levels of distress. A large literature links stress and emotional distress with increased cortisol output and depressions in immune function. In contrast, adaptive coping may decrease involuntary intrusive thoughts, potentially leading to a chain of events culminating in improved physiological processes. However, evidence supporting a pathway from adaptive coping and lower emotional distress to improved cancer outcomes must be considered highly speculative at this time.

A biopsychosocial model would suggest that effective psychosocial interventions can decrease involuntary stress responses and improve coping responses, putting in place the factors necessary to improve psychological and physiological outcomes. Although evidence exists to support a biopsychosocial model, no studies have fully evaluated pathways linking coping, distress, and physiological parameters relevant to breast cancer. The evidence to support an association of voluntary and involuntary stress responses with psychological adjustment in breast cancer is strong. Many studies have shown that the effectiveness of coping responses will influence the level of emotional distress. Coping strategies involving engagement with breast-cancer-related stressors predict better psychological adjustment, but disengagement strategies predict poorer adjustment (4). Similarly, a large body of research has demonstrated interactions among the brain, the neuroendocrine system, and the immune system. The evidence is strong linking emotional distress to cortisol and immune function in a general population; however, limited data exist specific to a breast cancer population, and it is not clear that knowledge gained from a healthy population can be generalized to a cancer population.

The importance of HPA axis and immune function in controlling the progression of breast cancer and minimizing rates of recurrence and mortality has been controversial. The precise influence of glucocorticoids and immune function on breast cancer development and progression is not clear. Conflicting findings have been reported from studies of the in vitro and in vivo effects of cortisol administration on tumor growth. Recent evidence concerning the involvement of the immune system in breast cancer development and progression hints at an important, yet not clearly understood, role. Impairments in immune function have been shown to be a poor prognostic indicator for breast cancer patients through associations with tumor size, nodal status, and metastatic status. The immune measures of T-cell proliferation and NK cytotoxic ability are among the best studied in terms of their associations with psychosocial factors, but they have not been as clearly evaluated for their associations with progression and long-term outcomes of breast cancer. Preliminary evidence shows them to be potentially important prognostic indicators; however, cause–effect relations cannot be determined. Similarly, only a few studies have shown elevated cortisol levels in breast cancer patients, and the cause–effect relations are unknown. Furthermore, alterations in cortisol and immune function caused by medical treatments are difficult to disentangle from influences by psychosocial factors.

Finally, although the evidence is strong that psychosocial interventions can have positive benefits on *psychological* adjustment, specific beneficial characteristics of interventions and the patients most likely to experience benefits have not yet been identified. Furthermore, evidence supporting the effects of psychosocial intervention on cortisol and immune function is extremely limited. Often, a large number of immunological-outcome measures are evaluated with what seem to be "hit or miss" results. Evidence of the effects of intervention on recurrence or survival is limited to four large-scale studies with metastatic breast cancer patients—one supporting the hypothesis of survival benefits and three failing to find survival benefits (11,99,109,110). Despite the initial promise associated with

early reports of improved survival in metastatic cancer patients receiving psychotherapeutic intervention, recent studies have failed to replicate findings, suggesting that survival advantages of psychotherapeutic intervention are small or nonexistent. In addition, survival studies with nonmetastatic breast cancer patients have not yet been reported.

FUTURE DIRECTIONS

There are several important directions for future research. First, much of the existing research on coping with stress has been conducted without a consistent, explicit definition of *coping*, making it difficult to make comparisons across studies. The manner in which coping is conceptualized necessarily influences the method of measurement, and as yet a consistent measurement of coping has not been used (112). Furthermore, specific attention needs to be given to the coping responses unique to women facing a diagnosis of breast cancer, as the most commonly used measurements of coping may not be appropriate with such a population.

Second, although Meyer and Mark (94) found clear evidence for beneficial effects of interventions on psychosocial factors, *physiological* benefits for breast cancer patients are not clear. Existing research provides exciting preliminary evidence that psychosocial interventions can influence physiological outcomes relevant to cancer; however, further research is undoubtedly required to clarify effects and identify potential mechanisms.

Third, research is required to determine the characteristics of interventions associated with improved psychological or physiological outcomes or both. Adequate comparisons of the different forms of intervention across studies are complicated by wide variations in structure and duration of interventions, provider characteristics, sample characteristics, and outcome measures. Furthermore, most currently reported studies of the physiological benefits of psychosocial interventions have involved relatively small sample sizes, which may result in a lack of adequate statistical power.

Fourth, because of the wide variability in psychological adjustment to breast cancer, individual differences in response to psychosocial interventions need to be examined. It is not clear which patients are most likely to reap the benefits of intervention. Also, the intervention type likely to be effective may depend on unique patient characteristics. These questions require the development of empirically validated psychosocial interventions, and an evaluation of individual differences in responses to intervention, to identify women most in need of intervention and which intervention is most likely to be beneficial (113).

Finally, no existing studies prospectively examine the influence of psychosocial intervention on coping, psychological adjustment, and hormonal and immune function in breast cancer patients. Evidence reviewed in this article suggests that interventions focused on improving women's ability to cope with breast cancer diagnosis, treatment, and recovery may have beneficial effects on emotional adjustment and potentially on physiological processes. However, large-scale prospective studies are necessary to determine if physiological benefits of improved psychological adjustment are sufficient in magnitude to influence the course of breast cancer.

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