# Depressive Symptoms in Patients With Cancer: Does Cortisol Keep Cytokines From Singing the Blues?

**Abstract:** Depressive symptoms are common among patients with cancer, and both psychological stress and physiological factors have been implicated in the etiology of depression. Scientific progress in this area is challenged by the changing nature of psychological and physiological processes over the course of cancer diagnosis and treatment. The article by Wu and colleagues in the current issue of *Psychosomatic Medicine* provides an example of thoughtful consideration of the complex longitudinal relationships between psychological stress, physiology, and depressive symptoms. These findings are put into context by discussing broader challenges in this area, with a focus on the contribution of inflammatory processes caused by cancer and/or its treatment to depressive and related sickness behavior symptoms. We outline several regulatory pathways by which cortisol, inflammatory processes, and depressive symptoms may interact in the context of cancer and highlight implications of these interactions for tumor progression. Additional research is needed to delineate these pathways and advance scientific understanding of the biobehavioral mechanisms underlying depressive symptoms in the context of cancer, with important implications for the development of effective interventions for patients undergoing initial cancer treatment, as well as for long-term survivors. **Key words:** depressive symptoms, breast cancer, cortisol, proinflammatory cytokines, psychoneuroimmunology.

Receiving a cancer diagnosis is a profoundly stressful experience for most people, provoking existential concerns, threatening substantial physical suffering in the near or distant future, and disrupting relationships and routines. Stressful life events are a potent and well-documented risk factor for depression in healthy adults (1). Thus, heightened depressive symptoms might be expected as part of a frequently observed reaction to a significant life stressor such as a diagnosis of cancer, and clinically significant depression is observed in 10% to 30% of patients with cancer (2). In addition to the psychological reaction to a life-threatening disease, mounting evidence also highlights the role of inflammatory processes caused by cancer and/or its treatment in the etiology of depressive symptoms in this patient population (3,4). Thus, the experience of depressive symptoms in patients with cancer is a complex, dynamic, and heterogeneous phenomenon. However, depression in patients with cancer remains poorly understood with regard to both causes and consequences. Important to consider is the fact that 70% to 90% of patients undergoing cancer treatment do not develop clinical depression. Identifying the biological and behavioral factors linked to the risk of, and resilience to, depressive symptoms is highly important because different underlying biobehavioral substrates may suggest distinct recommendations for clinical symptom management and could guide precision cancer care. These biological substrates may also contribute to patients' risk of disease progression and metastatic spread of cancer, further underscoring the need for additional research (5). The goal of this editorial is to highlight emerging challenges and opportunities in this important and growing area of research.

The relationship between inflammatory responses and depressive symptoms has received increasing empirical attention. In the context of cancer, proinflammatory cytokines are released by tumors and/or white blood cells in the tumor microenvironment in response to the cancer and/or tissue damage caused by treatment (6). These inflammation-related processes are hypothesized to underlie depressive symptoms in some patients with cancer (7,8). In animal models, circulating proinflammatory cytokines activate the central nervous system to induce a well-characterized syndrome of behavioral changes known as "sickness behavior" (7). Sickness behaviors, which include fatigue, decreased appetite, cognitive impairments, sleep disturbance, increased pain sensitivity, and social withdrawal, are also observed in humans during acute infections and after an experimental administration of inflammatory stimuli such as endotoxin (9). Notably, sickness behavior overlaps considerably with symptoms of depression. There is cross-sectional evidence linking inflammatory markers to depressive symptoms in some cancer patient populations (10–12), and several recent longitudinal studies support the role of cancer-related inflammatory processes in patients' experiences of depressive symptoms (13,14).

The effect of psychological stress on the cancer-inflammation relationship has received relatively little empirical attention, despite significant levels of distress experienced by many patients with cancer and well-documented ability of stress itself to upregulate inflammatory factors (15). In animal models, social disruption exacerbates both the behavioral (i.e., depression-like) and biological (i.e., increased plasma interleukin 6 and corticosterone) effects of interferon-α (16). In experimental studies with healthy humans, immune challenge (i.e., typhoid vaccination) and psychological stress synergistically increase interleukin 6 and negative mood (17). Early life stressors may also play a synergistic role in the relationship between depressive symptoms and inflammatory processes. For example, female adolescents exposed to childhood adversity show significant relationships between depressive symptoms and inflammatory factors, whereas those not exposed to early life stress do not (18). These interactions warrant careful consideration in the context of cancer.

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## EDITORIAL COMMENT

The article by Wu and colleagues (19) in the current issue of *Psychosomatic Medicine* provides an example of thoughtful consideration of the complex longitudinal relationships between psychological stress, physiology, and depressive symptoms. The authors examined the relationship between depressive symptoms and stress hormones in women with Stage II or III breast cancer for 1 year. Using a shortened version of the Center for Epidemiologic Studies–Depression Scale, they found that depressive symptoms shortly after surgery were inversely related to serum cortisol. However, women who reported higher depressive symptoms exhibited greater increases in serum cortisol over the year. This depression questionnaire contains only two neurovegetative symptoms, so the authors argue that the results were therefore unlikely to be due to cancer-related physical symptoms. The authors also considered the role of perceived stress and report that stress did not account for the relationship between depressive symptoms and cortisol. Wu et al. suggest that cortisol may buffer against negative emotions in the acute aftermath of diagnosis and surgery but that this protective effect "faded over the first year as stress decreased."

These findings are interesting to consider in the context of the broader literature on depressive symptoms and hypothalamic-pituitary-adrenal (HPA) axis activity. In healthy adults, depression has generally been associated with elevated levels of cortisol (20). A positive association between depressive symptoms and cortisol has also been observed in some cross-sectional studies of patients with cancer (10,11,21), although inverse associations between depressive symptoms and cortisol have also been reported in a few studies of patients with breast cancer (e.g., depressive symptoms associated with lower waking salivary cortisol levels in women with Stage IV cancer (22); history of depression [with or without current or past posttraumatic stress disorder] associated with lower morning plasma cortisol in newly diagnosed patients with breast cancer (23)). As Wu and colleagues point out, these earlier studies were limited by cross-sectional designs, and cortisol may protect patients from depressive symptoms under conditions of high stress (i.e., soon after diagnosis and surgery). But may be associated with elevated depressive symptoms as the acute stress phase abates. Although Wu et al. did not find that perceived stress (via the Perceived Stress Scale) accounted for their findings, they did not explore potential interactions between stress and cortisol as a predictor of depressive symptoms, or consider other related constructs (e.g., exposure to stressful life events). Nevertheless, as the first study to examine whether relationships between depressive symptoms, cortisol, and stress change over the course of breast cancer treatment, this article represents an important contribution to this growing field.

Wu et al. did not report on the role of inflammatory factors or other biological mechanisms by which cortisol might buffer mood. Glucocorticoids typically terminate the inflammatory cascade. Thus, in the aftermath of cancer surgery, elevated cortisol may restrain inflammatory cytokines that would otherwise contribute to depressive symptoms and other sickness behavior symptoms, resulting in the observed inverse association between cortisol and depressive symptoms. It has been demonstrated that prolonged exposure to high levels of cortisol can cause cells to develop glucocorticoid resistance, becoming less sensitive to the inhibitory effects of cortisol on inflammatory processes (24). As a result, under conditions of chronic cancer-related stress, elevated cortisol may fail to dampen inflammatory responses to adjuvant treatment, increasing risk for depressive symptoms and other sickness behavior symptoms and leading to a positive association between cortisol and depressive symptoms later in the cancer trajectory. This explanation for the findings reported by Wu et al. remains speculative but warrants consideration in future longitudinal studies.

Three interrelated pathways by which cortisol, inflammatory factors, and depressive symptoms may be elevated in the context of cancer are outlined in Figure 1. In the first pathway (Pathway 1), psychological stress associated with cancer leads directly to elevated depressive symptoms. Concurrently, cancer-related stress has downstream effects on the hypothalamic adrenal (HPA) axis, including prolonged increases in cortisol and down-regulation of the glucocorticoid receptor (1). In the second pathway (Pathway 2), increases in tumor-related or treatment-induced proinflammatory cytokines act on the central nervous system to trigger depressive symptoms and sickness behavior (3,4). These inflammatory processes also stimulate increased secretion of cortisol, which shuts down cytokine secretion in the periphery via a well-established negative feedback loop (that may become less effective under conditions of chronic stress and consequent glucocorticoid resistance) (25). Adding further complexity to this model, psychological stress may activate the same inflammatory processes in white blood cells and tumor cells via increased sympathetic activity (Pathway 3), and this sympathetically mediated inflammation may also contribute to elevated depressive symptoms. Support for this latter pathway is found in experimental studies with tumor cells, animal models, and humans (26,27), although it should be noted that depending on costimulatory factors present, sympathetic activity can also suppress inflammatory processes (28). Over time, as an individual is confronted with repeated or prolonged cancer-related stressors and evolving cancer treatment and tumor burden, all three of these pathways may act in synergy to increase circulating cortisol, inflammatory cytokines, and, ultimately, depressive symptoms. An additional fast regulatory loop to control proinflammatory responses has been proposed, involving activation of vagal afferents in response to peripheral cytokines and efferent inhibitory cholinergic feedback (29), but this mechanism has as yet received little research attention in patients with cancer.

Delineating the biobehavioral underpinnings of depressive symptoms in patients with cancer is no small feat, given the heterogeneity of both cancer and depressive symptoms, the complex interrelationships between physiological systems involved in these conditions, and the changing nature of psychological and biobehavioral processes over the course of evolving cancer and its treatments. It is clear that prospective longitudinal assessments and intervention studies are needed to advance the field. However, with the temporal trajectories of these pathways as yet not clear, researchers will need to find

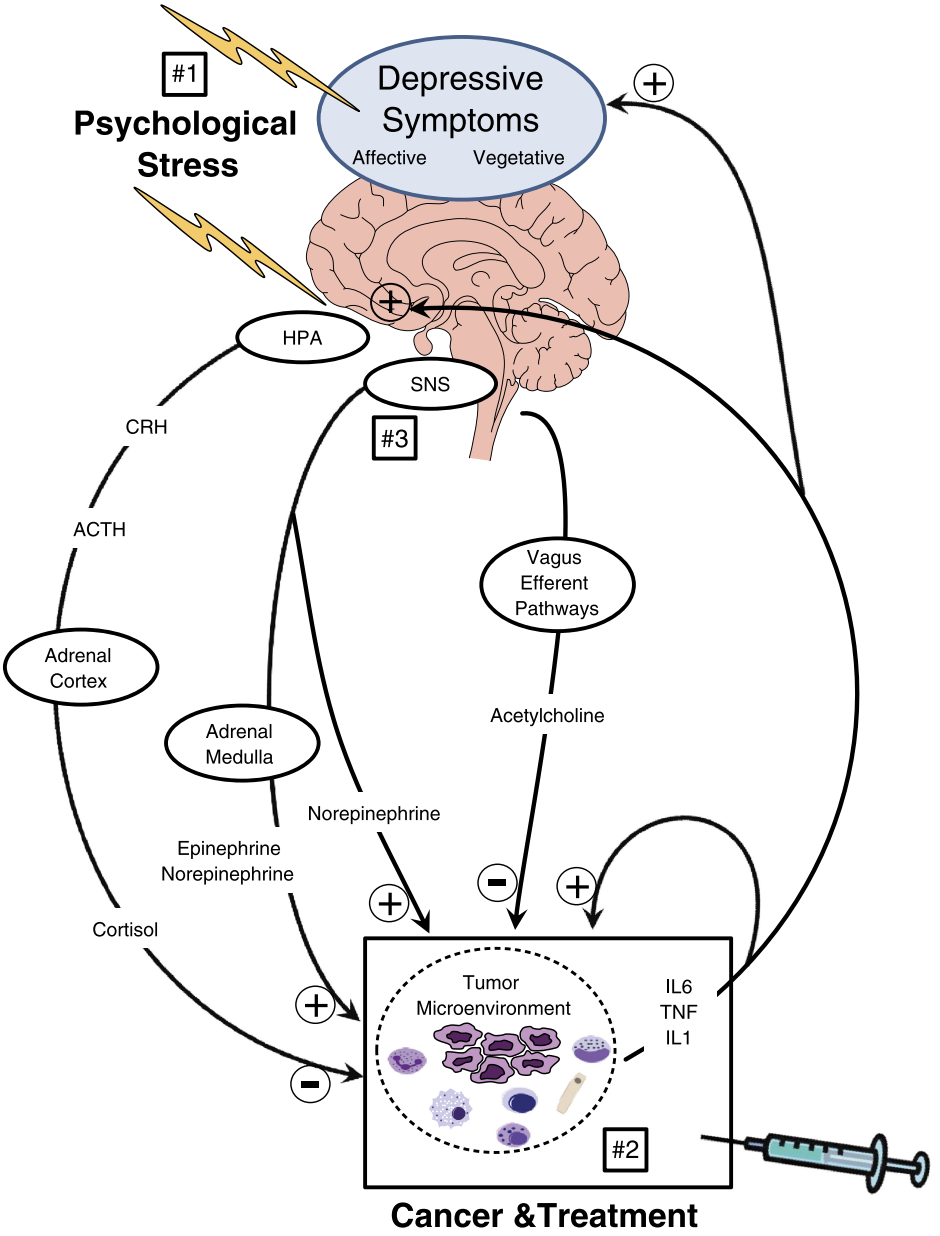


Figure 1. Interrelated pathways linking stress, cortisol, depressive symptoms, and inflammatory processes in patients with cancer. In the context of cancer, psychological stress can contribute to increased depressive symptoms directly via effects in the CNS or indirectly via effects on peripheral pathways. In Pathway 1, psychological stress associated with cancer diagnosis contributes directly to depressive symptoms while concurrently stimulating HPA activity, resulting in increased systemic cortisol levels. Although cortisol initially restrains ongoing inflammatory processes, chronically elevated cortisol levels result in down-regulation of the glucocorticoid receptor and reduced anti-inflammatory effects. In Pathway 2, tumor and/or treatment results in increased systemic proinflammatory cytokines, which reach the CNS and trigger depressive symptoms as well as increased HPA activity and increased systemic cortisol levels. These effects are enhanced in the context of chronic stress due to reduced sensitivity of the usual negative feedback loop between proinflammatory cytokine production and systemic cortisol. In Pathway 3, psychological stress associated with cancer stimulates SNS activity, which increases inflammatory processes in the periphery, increasing systemic proinflammatory cytokines that can again trigger depressive symptoms as well as increased HPA activity. Over time, all three of these pathways may act in synergy, resulting in glucocorticoid resistance, elevated inflammatory cytokines, and increased depressive symptoms. These factors create a favorable environment for tumor growth and progression. Of note, psychological stress may also lead to vagal withdrawal, reducing cholinergic inhibition of inflammation and resulting in increased cancer-related inflammatory responses. CNS = central nervous system; HPA = hypothalamic-pituitary-adrenal; SNS = sympathetic nervous system; CRH = corticotropin-releasing hormone; ACTH = adrenocorticotropic hormone; IL = interleukin; TNF = tumor necrosis factor. To view image in color, please visit: www.psychosomaticmedicine.org.

a balance between plans for frequent repeated assessments of patient-reported and biological variables and minimizing burden to patients with cancer. Further complicating assessment and analyses is the lack of clarity on the covariates that are most critical to consider, which may include changing medications, history of mood disorder, body mass index (which may also fluctuate over the cancer trajectory), and early life and concurrent psychological stressors. Another methodological issue as yet unresolved is how to select the most reliable, robust measures of key constructs (e.g., depressive symptom subsets,

such as neurovegetative versus affective symptoms; operationalization of glucocorticoid resistance and HPA dysregulation) that will permit translation of findings to clinical interventions.

With reports from the World Health Organization projecting a 57% surge in cancer incidence over the next two decades, identifying strategies to minimize depressive symptoms and optimize quality of life for patients with cancer is a pressing public health need. Psychosomatic medicine and biobehavioral oncology researchers are uniquely positioned to develop interventions targeting both behavioral and biological pathways involved in cancer progression and treatment. More interdisciplinary longitudinal studies like that of Wu et al. are needed to understand how psychological stress and coping interact with physiology to affect the health of patients with cancer and how to capitalize on these findings to enhance well-being.

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