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Abstract	The notion that psychological factors affect cancer has been present throughout history. Stress is an important factor that dysregulates immune function. Considerable work over the past decade has shown how psychological processes can impact pathways implicated in cancer progression. Furthermore, immune system dysregulation may have major implications for fatigue and depressive symptoms among cancer survivors. In this chapter, we first review evidence linking psychosocial factors to cancer incidence and progression. Then, we examine underlying biological mechanisms that may contribute to these links. Finally, we explore how dysregulated immune function contributes to cancer survivors' quality of life.

1 Psychoneuroimmunology and Cancer: Incidence, Progression, and Quality of Life

Christopher P. Fagundes, Monica E. Lindgren, and Janice K. Kiecolt-Glaser

Psychoneuroimmunology and Cancer: Incidence, Progression, and Quality of Life

The notion that psychological factors affect cancer has been present throughout history [1]. The immune system plays a critical role in cancer incidence, progression, and quality of life; thus, the field of psychoneuroimmunology has been at the forefront of these investigations. Stress is an important factor that dysregulates immune function [2]. In this chapter, we first review evidence linking psychosocial factors to cancer incidence and progression. Then, we examine underlying biological mechanisms that may contribute to these links. Finally, we explore how dysregulated immune function contributes to cancer survivors' quality of life, particularly fatigue and depression.

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Psychosocial Links to Cancer Incidence and Progression

Evidence suggests that psychological factors may be related to cancer incidence. A meta-analysis of 165 studies linked stress-related psychosocial factors with cancer incidence among those who were initially healthy [3]. For example, women who experienced stressful life events such as divorce, death of a husband, death of a relative or close friend during a 5-year baseline period were more likely to be diagnosed with breast cancer during the next 15 years than those who did not experience these events [4]. In a prospective study of men and women aged 71 and over, those who were depressed over three separate time points were more likely to develop cancer than those who were not [5].

Although links between psychosocial factors and the onset of cancer exist, there is much stronger evidence that psychological factors play an important role in cancer progression and mortality [6, 7]. For example, metastatic breast cancer patients who reported no past traumatic events had longer disease-free intervals than those who experienced one or more traumatic events [8]. Early stage breast cancer patients who were more hopeless about their cancer were more likely to relapse within 5 years compared to those who were less hopeless [9]. In the same study, women who were more depressed were more likely to die within 5 years compared to those who were less depressed [9]. Hepatobiliary carcinoma patients

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who had higher levels of depressive symptoms at diagnosis had 6–9 months shorter survival than those who were less depressed [10]. A recent meta-analysis of 25 studies revealed that mortality rates are 39% higher among breast cancer patients diagnosed with major or minor depression compared to those not depressed [11].

Animal studies provide experimental evidence for relationships between stress and cancer, allowing for stronger causal inferences. Restraint is a common stressor in animals. Among rats who were exposed to a carcinogen, those who underwent a restraint stressor were more likely to develop a cancer tumor than those who were not restrained [12]. Furthermore, rats who were unable to escape restraint had earlier incidence of tumors, larger tumors, and lower survival time compared to rats who were able to escape [13].

In sum, there is considerable evidence that psychosocial factors play an important role in cancer. However, many well-designed studies have failed to find such links [11]. Given the many factors that contribute to cancer incidence and progression, this may not be surprising [14]. Accordingly, testing biologically plausible models that link psychosocial factors with cancer can help identify possible mechanisms underlying these associations [7].

Psychological Factors and Cancer Progression

One likely mechanism linking psychosocial outcomes to cancer progression is dysregulated immune function; stress can suppress cellular immune function and enhance inflammation [2]. The autonomic nervous system (ANS) and hypothalamic–pituitary–adrenal (HPA) axis compose the two major pathways by which stress dysregulates immune function. Lymphocytes, macrophages, and granulocytes have receptors for products secreted by the ANS and HPA axes [15]. Norepinephrine and epinephrine, catecholamines that are released by the sympathetic nervous system during stress, can promote tumor cell proliferation [16].

In the vast majority of cases, cancer becomes life threatening when it metastasizes. Metastasis occurs when cancer cells penetrate lymphatic and blood vessels, circulate through the blood stream, and then spread into other organs [16]. In order for metastasis to occur, blood vessels must grow new networks to the site of the tumor, a process known as angiogenesis.

Vascular endothelial growth factor (VGEF) is an important angiogenesis promoting agent that is first synthesized inside tumor cells and then secreted into surrounding tissue [17]. When VEGF binds to its receptor, a signal is transmitted into the endothelial cells, promoting endothelial cell growth [14]. This leads to the creation of new blood vessels that fuel the tumor. Catecholamines can modulate VEGF. For example, in several cell lines, both norepinephrine and epinephrine modulated the expression of VEGF [18, 19]. However, these effects were blocked by a beta-antagonist, an agent that inhibits sympathetic nervous system response [20].

Psychological factors can also modulate VEGF. Ovarian cancer patients who reported receiving more social support had lower levels of VEGF both in their serum and tumor tissues than those receiving less social support [21, 22]. Furthermore, colon cancer patients who were lonelier and/or depressed had higher levels of serum VEGF than those who were less lonely and/or depressed [23, 24].

When VEGF activates endothelial cells they produce matrix metalloproteinase (MMPs) enzymes, a family of matrix-degrading enzymes that contribute to angiogenesis by promoting endothelial cell migration [25]. Catecholamines stimulate secretion of MMPs by both tumor and stromal cells. Higher levels of stress and depression, as well as lower levels of social support, were associated with elevated MMP-9 among women with ovarian cancer [22]. Two in vitro studies provided additional support and mechanistic evidence. In one study, norepinephrine enhanced MMP production, and increased the in vitro invasive potential of ovarian cancer cells by up to 189% [26]. These effects were blocked by beta-antagonists [26]. In another

study, norepinephrine increased MMP-2 and MMP-9; the invasiveness of these cells were blocked using an MMP inhibitor and the beta-antagonist propranolol [20].

Proinflammatory cytokines such as interleukin 6 (IL-6) and IL-8 also promote angiogenesis. Norepinephrine stimulates the production of IL-6 and IL-8 in ovarian cancer and melanoma cell lines [18, 27]. Women with ovarian cancer who reported receiving less social support had higher serum IL-6 levels compared to those who received more social support [28]. This same association was also found at the site of the tumor [28].

Inflammation induces macrophages to shift from a phagocytic phenotype to a pro-tumor phenotype. Tumor associated macrophages (TAMs) promote tumor growth and invasion, and simultaneously downregulates adaptive immunity [29]. Excessive TAM proliferation is associated with poorer survival [30]. Using in vivo models of breast cancer tumors, pharmacologic activation of the sympathetic nervous system initiated the recruitment of additional TAMs to the primary tumor, while also promoting further pro-tumor macrophage differentiation [31]. The beta-blocker propranolol reversed the stressed-induced macrophage infiltration and inhibited tumor spread [31].

Cancer cells must resist anoikis, programmed cell death, in order to spread to other organs [32]. Anoikis is inhibited by beta-adrenergic activation of the cell adhesion enzyme, focal adhesion kinase (FAK; pFAKy397) [32]. Ovarian cancer patients with high levels of intratumoral norepinephrine also had elevated levels of pFAKy397 in their tumors [32]. Additionally, epinephrine reduced sensitivity to apoptosis in prostate and breast cancer cell lines [33].

Stress alters natural killer (NK) cell activity, an important antitumor defense [34]. Breast cancer survivors who reported greater distress during 18 months after surgery had poorer NK cell activity than those who were less distressed [35]. Furthermore, the survivors from this cohort who experienced faster emotional recovery following surgery showed greater improvements in NK cell activity compared to the women who recuperated more slowly [36]. Men with localized prostate cancer who were more optimistic had greater NK cell cytotoxicity than those who were less optimistic [37].

Tumors can evade recognition and destruction by interfering with immune cell signaling. Accordingly, studies have considered the effect of stress on immune markers within the tumor microenvironment. Ovarian cancer patients who had more social support had greater NK cell activity in tumor infiltrating lymphocytes than those who had less support. Furthermore, those who were more distressed had poorer NK cell activity in tumor infiltrating lymphocytes than those who were less distressed [38, 39].

Gene Regulation

Biobehavioral factors are important in tumor gene expression [40]. Higher levels of depression and lower social support were associated with the upregulation of over 200 gene transcripts involved in tumor growth and progression [40]. Interestingly, ovarian tumors from women with higher levels of depression and lower levels of social support produced more norepinephrine compared to those with lower levels of depression and higher social support [40]. These findings suggest that psychosocial factors can impact cellular functioning, even at the molecular level.

Glucocorticoids

Glucocorticoids can impact cancer progression, as well as immunosurveillance. Glucocorticoids enhance tumor cell survival, downregulate the expression of DNA repair genes in breast cancer cells, and inhibit apoptosis following chemotherapy in breast cancer cells [41–43]. Additionally, cortisol can stimulate the growth of prostate and mammary cancer cells [44]. Prior to recurrence, breast cancer survivors who had higher levels of salivary cortisol were more likely to experience breast cancer reoccurrence compared to those who remained disease-free [45].

Circadian rhythm and cortisol production can be disrupted by psychological stress as well as sleep disturbances [46]. Long-term survival was shorter among breast cancer patients who had blunted circadian cortisol rhythms resulting from frequent nocturnal awakenings [46]. High plasma cortisol levels and depression were independently associated with suppressed immune responses to specific antigens in a separate sample of breast cancer patients (Sephton, Dhabhar et al. 2009). Furthermore, diurnal cortisol disruption has been noted in breast cancer patients exhibiting greater functional disability, fatigue, and depression [47].

Oncoviruses

Viral infections can initiate tumorigenesis, and stress hormones influence the activity of various human tumor viruses [48]. Elevated antibody titers to a latent herpesvirus reflect poorer cellular immune system control over virus latency. Psychological stress and depression can drive latent virus reactivation or replication by impairing the ability of the cellular immune system to control viral latency [49]. For example, the heightened antibody titers to latent herpesviruses reported during academic exams, particularly EBV and HSV-1, appear to reflect alterations in the competence of the cellular immune response [50–52].

Human papilloma viruses (HPVs) establish infections in the stratified epithelium of the skin or mucous membranes and can cause genital warts. Almost all cervical cancers are caused by HPVs [53]. HPVs initiate tumor-supporting genetic and immunological changes when activated by glucocorticoids [48]. Stressful life events are a risk factor for increased progression of cervical dysplasia in HPV-positive women [54, 55].

Following infection with human immunodeficiency virus 1 (HIV1), catecholamines can accelerate AIDS-associated malignancies by increasing systemic susceptibility [48]. For example, people with heightened sympathetic nervous system activity are at increased risk for AIDS-associated B-cell lymphomas [56]. Catecholamines can also activate Kaposi sarcoma-associated herpesvirus by similar mechanisms to those that activate human T-cell lymphotropic viruses 1 and 2, two cancer-related viruses relevant to AIDS-patients [57, 58]. Stress hormones can thus impact a variety of cell-mediated immune responses affecting both the recognition of tumor viruses and the immunological defense against them.

In a study from our own lab that addressed the joint impact of social support and SES (indexed by education) in women who were dealing a potential or an actual breast cancer diagnosis, more highly educated women who had more support from friends had lower EBV antibody titers, reflecting better cellular immune function; however, for less educated women, friend support was not associated with EBV antibody titers [59]. This finding is health-relevant because recent research has highlighted links between herpesvirus reactivation and inflammation [60].

Quality of Life and Inflammation among Cancer Survivors

Thus far we have focused exclusively on how psychosocial factors interact with the immune system to contribute to cancer incidence and progression. However, over the past decade, some of the most promising work in the field of psychoneuroimmunology and cancer has focused on how the immune system interacts with the brain to contribute to cancer survivors' quality of life. Most of this work has focused on how inflammation contributes to sickness behaviors, fatigue, and depressive symptoms in breast cancer survivors.

Physically ill humans and animals exhibit sickness behaviors when exposed to an infection. Sickness behaviors are functional in that they help sick individuals restructure their perceptions and actions in order to conserve energy and resources [61]. Although feeling tired and lethargic is a normal and adaptive response to an acute infection, persistent low-grade inflammation has been linked to fatigue and depression [61]. Fatigue and depression can be side effects of long-term low-grade inflammation, representing

a maladaptive version of inflammatory-induced sickness behaviors [61].

Proinflammatory cytokines can access the brain through a variety of key pathways including the leaky regions in the blood–brain barrier (e.g., circumventricular organs), cytokine-specific transport molecules expressed on brain endothelium, and vagal afferent fibers [62]. Proinflammatory cytokines act on the brain to facilitate sickness behaviors by reducing connectivity of brain areas associated with lethargy [63]. Furthermore, cytokines modify people's serotoninergic systems by increasing idoleamine 2,3 (IDO), reducing tryptophan production, and thus eventually serotonin levels [61]. In a separate pathway, proinflammatory cytokines can also influence HPA axis hormones that are associated with mood regulation, an indirect route [64].

Fatigue and Cancer Survivors

Fatigue is the most common problem among long-term cancer survivors [65], as well as the symptom that interferes most with daily life [66, 67]. Fatigue adversely affects overall quality of life, as well as many daily activities including mood, the sleep–wake cycle, and personal relationships [68–70]. Fatigue is a normal and expected response to chemotherapy and radiation [71]. However, fatigue persists many years beyond cancer treatment in a substantial number of cancer survivors [72]. Long-term fatigue among breast cancer survivors is particularly notable. For example, in a longitudinal study of 763 breast cancer survivors, 34% were fatigued 5–10 years after diagnosis, compared to 35% 1–5 years after diagnosis; 21% of the women were fatigued at both assessments, suggesting more severe or persistent fatigue among a significant proportion of cancer survivors [65]. Most studies addressing relationships between the immune system and fatigue have focused exclusively on breast cancer survivors.

In general, neither disease type nor treatment variables have demonstrated reliable associations with fatigue in cancer survivors. Specifically, type of cancer, disease stage at diagnosis, tumor size, number of nodes involved, presence and site of metastases, time since diagnosis, the type or extent of cancer treatment (including chemotherapy regime, dose, and cycles, and type of radiation), length of treatment, and time since treatment completion do not consistently predict the occurrence or severity of fatigue among survivors [72].

Bower and her colleagues have demonstrated that post-treatment breast cancer-related fatigue is associated with elevated inflammation. Breast cancer survivors with persistent post-treatment had higher levels of soluble inflammatory markers IL-1 receptor antagonist (IL-1ra), STNF-R11, and neopterin than breast cancer survivors who were not fatigued [69]. Interestingly, fatigue was not predicted by time since diagnosis or time since treatment. These findings were replicated in a subsequent study of fatigued and non-fatigued breast cancer survivors such that those who were fatigued had higher levels of soluble markers of proinflammatory cytokines than non-fatigued survivors (i.e., IL-1ra and soluble IL-6 receptor) [73].

Stress promotes inflammatory responses [2]. Fatigued cancer survivors show greater increased cytokine production when stressed compared to nonfatigued cancer survivors. Fatigued breast cancer survivors had greater increased LPS-stimulated IL-1β (beta) and IL-6 production from baseline to 30 min after the Trier Social Stress Task (TSST) than non-fatigued survivors [74]. Those who were fatigued also had greater increased CD4+ T lymphocytes compared to their non-fatigued counterparts [74].

In sum, fatigued breast cancer survivors show higher levels of resting and stress-induced stimulated proinflammatory cytokine levels compared to non-fatigued breast cancer survivors. However, less is known about whether inflammation is associated with fatigue in other types of cancer. Furthermore, little is known about the physiological mechanisms underlying persistent fatigue and inflammation.

Alterations in immune regulatory systems that are linked to inflammation may play an important role in fatigue [75]. Fatigued cancer survivors had 31% more circulating T-cells compared to non-fatigued cancer survivors. However, there were no alterations in circulating B-cell numbers [73].

Similarly, in another study, fatigued cancer survivors had elevated CD4+ T lymphocytes in contrast to nonfatigued cancer survivors [73]. Alterations in inflammatory markers may come from differences in the cellular immune response.

Autonomic nervous system functioning is linked to inflammation and may play a role in cancer related fatigue. Activation of the sympathetic branch of the autonomic nervous system enhances inflammation. As previously mentioned, stress heightens production of the catecholamines epinephrine and norepinephrine by the sympathetic nervous system. Norepinephrine induces nuclear factor-kappa B (NF-κB) transcription, which enhances proinflammatory cytokine production [76]. The parasympathetic branch of the autonomic nervous system works in opposition to the sympathetic branch. Higher parasympathetic activity can lower inflammation by inhibiting proinflammatory cytokine production [77]. Therefore, the combination of lower parasympathetic activity and higher sympathetic activity results in elevated inflammation.

In a recent study from our own lab, breast cancer survivors who reported more fatigue had significantly higher norepinephrine and lower heart rate variability (a measure of parasympathetic activity) than their less fatigued counterparts [78]. Fatigue was not related to treatment or disease variables including treatment type, cancer stage, time since diagnosis, and time since treatment [78]. Importantly, the relationship between HRV and cancer-related fatigue was sizeable. Based on research that has demonstrated characteristic age-related HRV decrements, the findings suggested a 20 year difference between fatigued and non-fatigued cancer survivors based on their HRV pattern, raising the possibility that fatigue may signify accelerated aging [78]. Given that both HRV and norepinephrine promote inflammatory responses, the findings may be tapping into the same physiological substrate that links proinflammatory cytokines to cancer-related fatigue and sickness behavior.

Cortisol acts to inhibit the release of proinflammatory cytokines. Cortisol peaks early in the morning and then decreases throughout the day [69]. In one study, breast cancer survivors had lower levels of morning serum cortisol than non-fatigued controls [69]. In another study, fatigued breast cancer survivors had flatter cortisol slopes across the day than non-fatigued survivors, as well as a rapid decline in cortisol levels in the evening among fatigued survivors [79]. Accordingly, these studies implicate both autonomic and HPA function in cancer-related fatigue and inflammation [78, 79].

Depression and Cancer Survivors

Cancer patients are three to five times more likely to experience major depression than non-cancer patients [80–82]. Major depression impairs cancer patients' quality of life as well as treatment adherence [80–82]. The immune system may play an important role in the etiology of cancer-related depression.

Although there is ample evidence that depressive symptoms can elevate inflammatory levels, there is also considerable evidence that proinflammatory cytokines contribute to depressive symptoms [64]. The association between inflammation and depressive symptoms has been found in a variety of different aging and diseased populations, including cancer survivors [83–86]. In a study of 114 patients with breast, lung, head and neck, or GI cancer, those who met criteria for clinical depression had higher levels of IL-6 compared to those that did not [87]. Another study of pancreatic, esophageal, and breast cancer patients demonstrated similar results [86].

Interferon, a proinflammatory cytokine, is used for the treatment of infectious diseases and some cancers. Between 20 and 50% of patients who receive interferon therapy develop significant depressive symptoms [86]. IFN-α-induced increases in IL-6 were positively related to increased depressive symptoms and anxiety over a 1-month period [88].

Experimental work provides additional evidence that inflammation induces depressive symptoms. Healthy volunteers who were injected with *Salmonella typhi* vaccine had increased post-vaccination levels of IL-6, IL-1ra, tumor

necrosis factor-α (alpha) (TNF-α (alpha)), and negative mood compared to pre-vaccination levels compared to those injected with a placebo [89]. Antidepressants may be an effective strategy to minimize these negative consequences. In a double blind placebo-controlled trial, those who took a TNF-α (alpha) antagonist for the treatment of psoriasis had significant improvement in depressive symptoms compared with placebo-treated individuals [90].

Psychosocial Interventions and Biological Outcomes in Cancer

Many interventions have been developed to reduce cancer-related distress [91]. Given that depression and stress impact cancer biology, psychosocial interventions may impact cancer-related outcomes. Behavioral and psychosocial interventions for cancer patients have included cognitive-behavioral and stress management therapies, support groups, and psychoeducation [91].

Interventions that enhance social support, teach relaxation, and coping can improve neuroendocrine and cellular immune functioning. A 10-week, 10-session cognitive-behavioral stress management (CBSM) intervention reduced anxiety and depression, decreased social disruption, and increased benefit finding in women with stages I–III breast cancer who were recruited post-surgery [92]. Furthermore, compared to controls ($n=65$), women randomized to CBSM ($n=63$) had a significant decline in serum cortisol, greater Th1 cytokine production (interleukin-2 and interferon-y) and IL-2–IL-4 ratio after adjuvant treatment [92]. However, there were no group differences in CD4, CD8, CD56, CD56+CD3+, or CD19 cell counts [92]. Furthermore, there were no group differences for the ratio of interferon-y and IL-4 production [92].

A multicomponent biobehavioral intervention was designed to reduce emotional distress, improve health behaviors, and quality of life among 227 women who were treated for regional breast cancer. The baseline assessment occurred after surgery but before adjuvant therapy; the women participated in the intervention during adjuvant therapy. Those who received the intervention ($n=114$) perceived greater support and improved their dietary habits at the 4-month follow up compared to controls ($n=113$). Interestingly, among those who were assigned to the intervention group, T-cell proliferation remained stable or increased, while it declined in the controls [35]. However, there were no significant group differences in CD3, CD4, and CD8 counts [35].

Complementary and alternative-medicine interventions have also improved immunological function among cancer survivors. The standardized "healing touch" biotherapy (HT) is an alternative-medicine intervention designed to manipulate "energy fields" around the body to reduce symptom burden. In a randomized trial of 60 cervical cancer patients who were receiving chemotherapy and radiation, those who received HT ($n=21$) had higher level of NK cell cytotoxicity over the course of their treatment than those who did not ($n=39$) [93]. However, these changes did not parallel changes in NK cell number [93].

Caution should be exercised when interpreting psychosocial interventions that enhance immune function and cancer outcomes. As reviewed, there is evidence that psychosocial interventions may modulate immune function. However, many intervention studies have failed to show positive results [94]. Accordingly, more research is needed before definite conclusions are made.

Conclusion and Future Directions

Linkages between psychological factors and cancer have long been theorized, and researchers are now beginning to understand the mechanisms behind these links. Considerable work over the past decade has shown how psychological processes can impact pathways implicated in cancer progression. Furthermore, immune system dysregulation may have major implications for fatigue and depressive symptoms among cancer survivors.

Researchers have made great strides toward understanding how the brain and immune system interact to affect cancer survivors' quality of life

and possibly morbidity and mortality. However, the vast majority of these studies have focused on a small proportion of cancer types. Cancer interacts with the immune system differently depending upon cancer type [95]. Furthermore, the ways in which people are psychologically affected by cancer differ based on a variety of factors including prognosis, treatment type, and pain—which are largely determined by cancer type (as well as stage) [96]. Accordingly, researchers should expand their investigations to encompass a wider range of cancers. Finally, cultural and socioeconomic factors play an important role in every aspect of the cancer experience [97, 98]; however, researchers have devoted little attention to this issue. For example, cultural and socioeconomic factors may exacerbate stress induced immune dysregulation [7]. Understanding how these factors interact to contribute to cancer outcomes is a critical direction for future research.

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