Brian I. Carr
Jennifer Steel *Editors*

# Psychological Aspects of Cancer

## A Guide to Emotional and Psychological Consequences of Cancer, Their Causes and Their Management

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*He used to say:*
*If I am not for myself, who will be for me?*
*And if I am only for myself, what am I?*
*And if not now, then when?*
–Hillel Mishna Avot 1:14

*Who is wise? He who learns from every person*
–Ben Zoma Mishna Avot 4:1

For my daughters: Ophira and Feridey

# Preface

The idea for this book of essays arose after several years during which the co-editors collaborated at the University of Pittsburgh on the medical oncology and psychological care of patients diagnosed with hepato-biliary cancer. Although the need for patient psychosocial support was evident, the time available in an ever-busy clinic was not conducive to the extended discussions that many patients and families wanted. The time pressures on staff in U.S. hospitals are increasing annually, in the name of system and business efficiencies. We noted a dichotomy between ideal total patient care in clinical practice and the realities of limited time per patient for employees of medical organizations. To some extent, patient-enabling Internet communication and services with health-care providers are beginning to be introduced with this dichotomy in mind. Still, the need for real-time, face-to-face contact and sufficient time with health professionals to hear and address their concerns are a patient priority.

He medical/psychological literature has exponentially expanded in the last decade with increasing documentation and sub-set characterization of various aspects of the quality of life of patients and their loved ones. Moreover, feedback from patients has resulted in a further proliferation of research that has extended to family and caregivers, who are rightly seen as important components of the patient environment, as well as subjects in need of study and care in their own right.

The arrival of unwelcome health-related news in the form of a cancer diagnosis would be expected to interrupt a person's self-perception and plans for his or her unfolding life story. Reflection on this interruption will likely result in fear and anxiety about the unknown quality and quantity of life that will now lie ahead. The major part of this book is taken up by considerations of the available resources in support of patient coping with his or her post-diagnosis new life structure as it is imagined and might become. Much of that is hypothesis and world-view driven, as seen in section C. Constructing a post diagnosis new life structure involves concepts of hope, meaning, and spirituality and their various impacts on coping, which in turn may change during the development and course of an individual's disease. All of this is concerned with the various cognitive and emotional aspects of coping with cancer and flows logically from the expected effects of disease on a person's thoughts, hopes, plans, and feelings. An emerging concept, however, is the idea of the potential reversibility of this process, in which thoughts and emotions might

influence body function and disease development and its progression. For example, the concept that stress might be involved in and predisposing of cardiac ischemia and peptic dysfunction is very old. Evidence is emerging that these psychological and behavioral processes might also be involved in the development and/or progression of several chronic diseases, such as the inflammatory diseases and cancer. If mental processes can impact the immune and endocrine systems, then they might modulate the inflammatory and tumor growth processes that these systems mediate.

This book opens with two essays on the biological basis of emotion/mental-driven body processes and disease. The consequence of such considerations is that since thoughts and emotions can be modulated and changed with assistance from health-care professionals, then psychological counseling might be seen not only to help patients cope, but possibly to influence the disease itself. The book then proceeds to a section on genetic predispositions to cancer and the psychological considerations involved in screening and preemptive therapies and decision-making in cancer therapy. The third section deals with the philosophical and religious underpinnings of psychological factors involved in coping with disease state stressors and the roles of hope in coping. The fourth section is an acknowledgement that patients live in a social context, which often includes a partner and/or caregiver. The fifth section includes several essays on aspects and modalities of caregiving that are designed to help patients coping with their cancer and its aftermath, which increasingly extends for years. This is followed by a section with some considerations of approaches to dying and concerns of those who are left behind. The last section seeks to tie all this together and provide a resource chapter.

This book is not intended as a textbook, but as a set of essays for both health-care professionals and all people whose lives are directly or indirectly affected by cancer, to provide a sense of the activity and several new concepts in the rapidly expanding field of psychological support and psycho-social needs and context of the patient with cancer.

The book is presented in 7 sections: A. Biological basis; B. Prevention and decision-making; C. Theory in psychosocial oncology; D. The social context; E. Patient support; F. Advanced cancer: G. Wide-angle lens: resources and overview.

Puglia, Italy and Philadelphia, PA Brian I. Carr

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

1

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

## Psychoneuroimmunology and Cancer

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, or 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 downregulate 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 [47]. Furthermore, diurnal cortisol disruption has been noted in breast cancer patients exhibiting greater functional disability, fatigue, and depression [48].

### Oncoviruses

Viral infections can initiate tumorigenesis, and stress hormones influence the activity of various human tumor viruses [49]. 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 [50]. 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 [51–53].

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 [54]. HPVs initiate tumor-supporting genetic and immunological changes when activated by glucocorticoids [49]. Stressful life events are a risk factor for increased progression of cervical dysplasia in HPV-positive women [55, 56].

Following infection with human immunodeficiency virus 1 (HIV1), catecholamines can accelerate AIDS-associated malignancies by increasing systemic susceptibility [49]. For example, people with heightened sympathetic nervous system activity are at increased risk for AIDS-associated B-cell lymphomas [57]. 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 [58, 59]. 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 [60]. This finding is health-relevant because recent research has highlighted links between herpesvirus reactivation and inflammation [61].

## 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 [62]. 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 [62]. Fatigue and depression can be side effects of long-term low-grade inflammation, representing

a maladaptive version of inflammatory-induced sickness behaviors [62].

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 [63]. Proinflammatory cytokines act on the brain to facilitate sickness behaviors by reducing connectivity of brain areas associated with lethargy [64]. Furthermore, cytokines modify people's serotoninergic systems by increasing idoleamine 2,3 (IDO), reducing tryptophan production, and thus eventually serotonin levels [62]. In a separate pathway, proinflammatory cytokines can also influence HPA axis hormones that are associated with mood regulation, an indirect route [65].

## Fatigue and Cancer Survivors

Fatigue is the most common problem among long-term cancer survivors [66], as well as the symptom that interferes most with daily life [67, 68]. Fatigue adversely affects overall quality of life, as well as many daily activities including mood, the sleep–wake cycle, and personal relationships [69–71]. Fatigue is a normal and expected response to chemotherapy and radiation [72]. However, fatigue persists many years beyond cancer treatment in a substantial number of cancer survivors [73]. 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 [66]. 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 [73].

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 [70]. 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) [74].

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 [75]. Those who were fatigued also had greater increased CD4+ T lymphocytes compared to their non-fatigued counterparts [75].

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 [76]. 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 [74].

Similarly, in another study, fatigued cancer survivors had elevated CD4+ T lymphocytes in contrast to nonfatigued cancer survivors [74]. 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 [77]. 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 [78]. 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 [79]. Fatigue was not related to treatment or disease variables including treatment type, cancer stage, time since diagnosis, and time since treatment [79]. 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 [79]. 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 [70]. In one study, breast cancer survivors had lower levels of morning serum cortisol than non-fatigued controls [70]. 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 [80]. Accordingly, these studies implicate both autonomic and HPA function in cancer-related fatigue and inflammation [79, 80].

## Depression and Cancer Survivors

Cancer patients are three to five times more likely to experience major depression than non-cancer patients [81–83]. Major depression impairs cancer patients' quality of life as well as treatment adherence [81–83]. 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 [65]. The association between inflammation and depressive symptoms has been found in a variety of different aging and diseased populations, including cancer survivors [84–87]. 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 [88]. Another study of pancreatic, esophageal, and breast cancer patients demonstrated similar results [87].

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 [87]. IFN-α-induced increases in IL-6 were positively related to increased depressive symptoms and anxiety over a 1-month period [89].

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 [90]. 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 [91].

## Psychosocial Interventions and Biological Outcomes in Cancer

Many interventions have been developed to reduce cancer-related distress [92]. 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 [92].

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 [93]. 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 [93]. However, there were no group differences in CD4, CD8, CD56, CD56+CD3+, or CD19 cell counts [93]. Furthermore, there were no group differences for the ratio of interferon-*y* and IL-4 production [93].

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 ($n=39$) [94]. However, these changes did not parallel changes in NK cell number [94].

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 [95]. 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 [96]. 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) [97]. 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 [98, 99]; 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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# Inflammation, Chronic Disease, and Cancer: Is Psychological Distress the Common Thread?

2

Feridey N. Carr and Elizabeth M. Sosa

Inflammation, the hallmark feature of immunological response to invading microbes, has been implicated in a growing list of major diseases, including rheumatoid arthritis and lupus, inflammatory bowel disease, pulmonary and cardiovascular diseases, obesity, and diabetes mellitus. The focus on chronic inflammation has intensified since it has been linked with specific types of cancer, particularly those associated with viral infection or an inflammatory response. Although some chronic diseases have long been acknowledged to increase risk of malignancies, it is only within the past decade that chronic inflammation has been hypothesized to be a key factor in the development of cancer. While there is as of yet little evidence to suggest that psychological distress, particularly chronic stress and depression, directly affects the pathogenesis of tumors, there is an increasing amount of scholarship indicating that psychosocial factors directly contribute to the development and maintenance of chronic inflammation. In fact, it is possible that while depression may contribute and increase the levels of circulating pro-inflammatory cytokines, inflammation may itself act on the brain to induce depressive symptomatology. This chapter focuses on the primary disease categories in which inflammation is a known contributor and discusses the mechanisms by which the inflammatory process interacts with carcinogenesis as well as psychological aspects of chronic inflammation. Some clinical considerations are offered for interventions targeting the anxio-depressive symptoms associated with major illness that may also disrupt the chronic inflammatory cycle and its resultant disease process.

## Inflammation and Cancer

In 1863, Rudolf Virchow hypothesized that cancerous tumors originated at sites of chronic inflammation within the human body [1]. Virchow identified the role of inflammation in carcinogenesis when he noticed the presence of leucocytes in neoplastic tissue and suggested that the "lymphoreticular infiltrate" reflected the origin of malignancies where inflammatory processes occurred [1]. Virchow's claim was not investigated for more than a century. Just recently, researchers have begun examining the hypothesized relationship and directing efforts to research the possible connection between chronic inflammation and cancer. Epidemiological studies have demonstrated that chronic inflammation predisposes individuals to a variety of cancers such as thyroid, bladder, cervical, prostate, esophageal, gastric, and colon [1, 2]. About 25% of all deaths from cancer worldwide are attributable to underlying infections and inflammatory

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responses [3]. Chronic infection and inflammatory responses are known to have associations with the development of certain cancers, such as the human papilloma virus (HPV) and its relationship to cervical cancer, or the infection of hepatitis B and C viruses leading to hepatocellular carcinoma (HCC) [4]. Increased risk of tumor growth is associated with chronic inflammation caused by microbial infections and autoimmune diseases (e.g., inflammatory bowel disease and the risk of colon and colorectal cancers), as well as inflammatory conditions resulting from uncertain origins such as prostatitis, which can lead to prostate cancer [5–7]. Chronic inflammation contributes to a tumor promoting environment through various avenues that may include cellular transformation, the proliferation and survival of malignant cells, development of angiogenesis and metastasis, reduction of adaptive immune responses, and tumor response to chemotherapeutic drugs and hormones [7]. The inflammatory response and resultant tumors may be conceptualized as wounds that do not heal [8].

The role of chronic inflammation in the development of cancerous tissue easily becomes convoluted with many aspects that must be considered such as the contributions of various inflammatory cells, mediators, and signaling pathways in cancer genesis [7]. The inflammatory process involves the presence of inflammatory cells and inflammatory mediators which include chemokines and cytokines in tumor tissues, tissue remodeling and angiogenesis [7]. The prime endogenous promoters include transcription factors such as nuclear factor-kappB (NF-kB) and signal transducer activator of transcription-3 (Stat3) as well as major inflammatory cytokines, such as Interleukin Beta (IL-1 b), Interleukin 6 (IL-6), Interleukin 23 (IL-23) and tumor necrosis factor alpha (TNF-a) [9–12]. TNF-a was the first factor isolated as an anticancer cytokine but at dysregulated levels within the immune system, its presence mediates a variety of diseases [13]. TNF-a has also been demonstrated to be a major predictor of inflammation [14]. Several pro-inflammatory cytokines have been related to tumor growth, indicating that inflammation is associated with carcinogenesis [1, 15]. These include IL-1, IL-6, IL-8, and IL-18. Interleukins are involved in different steps of tumor initiation and growth. Specifically, Negaard et al. demonstrated that individuals with hematological malignancies have increased bone marrow micro-vessel density as well as elevated levels of IL-6 and IL-8, possibly contributing to the malignant phenotype [16].

Chemokines are a family of proteins that play several roles in cancer progression, including angiogenesis, inflammation, and cell recruitment and migration. Chemokines also play a central role in leucocyte recruitment to sites of inflammation [1]. Most tumors produce chemokines that are one of two major groups, Alpha and Beta chemokines [1]. Evidence from murine models and human tumors propose that Beta chemokines contribute vastly to macrophage and lymphocyte infiltration in melanoma, carcinoma of the ovary, breast, and cervix, as well as in sarcomas and gliomas [1, 17, 18]. A key molecular link between inflammation and tumor promotion and progression is transcription factor NF-kB, which regulates TNF, interleukins, chemokines, and other molecular factors [9]. Although NF-kB is inactive in most cells, there is an activation state that is induced by a wide variety of inflammatory stimuli and carcinogens that, in turn, mediate tumorigenesis [19].

## Inter-relationship Between Depression and Inflammation

The relationship between the brain and the peripheral organs, often referred to as the "mind-body" connection, is based on alterations in the endocrine and immune systems that lead to the chemical changes that occur in clinical depression. Pro-inflammatory cytokines, particularly IL-6, have been found to occur in greater quantities in depressed patients [20]. It has also been shown that about 45% of patients being treated medically with pro-inflammatory cytokine interferon-alpha (IFNa) developed symptoms of depression that was reversed once the treatment ended [21]. Inflammation is not only a contributing factor in depression but also in many domains

of medical illness. Among patients diagnosed with major depression, there is evidence to suggest that relationships exist between severity and duration of depression and increased prevalence of other disease processes, such as cardiovascular disease, Type-2 diabetes, a variety of autoimmune diseases and cancer [22]. Major depressive disorders are also more prevalent in patients who suffer from illnesses that lead to chronic inflammation than healthy people [23]. While the presence of an inflammatory disease may initiate depressive symptoms in patients without preexisting psychological disorders, it is also the case that inflammation occurs in depressed patients who are not suffering from concurrent inflammatory disorders [24].

It is now known that the brain is not the "immune-privileged" organ that it was once presumed, as many thought it to be protected by the blood–brain barrier. Rather, the brain is very much influenced by the peripheral immune system where large molecules such as cytokines, chemokines and glucocorticoids originating in the peripheral organs can affect the neuronal pathways implicated in depression [20, 25]. Recently, it has been shown that symptoms of sickness (fatigue, decreased appetite, social withdrawal, disturbed sleep cycles, anhedonia and mild cognitive impairment), the normal bodily response to infection, are triggered by pro-inflammatory cytokines, including IL-1a and b, TNF-a and IL-6 [20]. These cytokines are responsible for developing the body's inflammatory (local and systemic) response to invading microbes. In doing so, they also impact neural circuitry within the brain, resulting in the behavioral symptoms of sickness. Such sickness behavior is remarkably similar to the symptoms of clinical depression. It is generally the role of anti-inflammatory cytokines to regulate the duration of these sickness symptoms, possibly by inhibiting pro-inflammatory cytokine production and interfering with pro-inflammatory cytokine signaling [26].

Despite the evidence to support the mechanism by which pro-inflammatory cytokines act on the brain, the directionality of the inflammation–depression relationship is as yet unclear. As mentioned earlier, there is also research to suggest that depression may predispose people to developing illness. One study attempting to examine the directionality of the inflammation–depression relationship found that baseline depression scores of healthy (no medical illness) patients independently predicted change in IL-6. In contrast, IL-6 did not predict change in depression score [27]. The implication of those findings suggests that depression in previously healthy people may lead to inflammation and inflammation may be the mechanism through which depression potentiates chronic illness.

## Rheumatic Disease

Rheumatic diseases, including rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) are autoimmune conditions that often involve periods of painful swelling and inflammation in the joints and muscles. The inflammatory stages of RA involve the infiltration by inflammatory cells of the synovial sublining, activating the production of pro-inflammatory cytokines, chemokines, and growth factors that results in synovial lining hyperplasia [28]. This process results in the hyper-activation of macrophage and fibroblast-like synoviocytes, which releases additional cytokines, chemokines, and growth factors [28]. This process leads to systemic inflammation and the production of enzymes that destroy the organized extracellular matrix [29]. IL-6, a cytokine that regulates the immune and inflammatory response, is thought to play pathologic roles in RA [30]. Increased IL-6 levels have been found in both serum and synovial fluid in patients with RA, and are also known to correlate with increased disease activity [31, 32]. Baecklund et al. examined disease activity and various secondary symptoms of rheumatic disease, as well as drug treatment to evaluate risk factors for the development of lymphoma, a cancer associated with RA [33]. In a nested case–control study with 41 patients and 113 controls, no association was found between any specific immunosuppressive drug and increased risk of lymphoma. However, a strong association was seen between disease

activity and risk of developing lymphoma. In a similar study, Baecklund et al. investigated both RA patient cancer risk and the danger of anti-rheumatic treatment in lymphoma development [34]. After comparing 378 RA patients positive for malignant lymphoma history with 378 healthy controls, data revealed that individuals with severe disease activity were at increased risk of lymphoma. In addition, increased level of pro-inflammatory cytokines, not drug treatment, predicted lymphoma risk.

Although RA patients' increased risk for developing malignant lymphomas is not completely understood, there are several possible hypotheses that have emerged, including the role of immunosuppression, Epstein-Barr virus infection, and unregulated systemic inflammation [33–39]. In one systematic review and meta-analysis, Smitten et al. characterized the associated risk of four site-specific malignancies that included lymphoma, lung, colorectal, and breast cancer in patients with RA [40]. Results indicated that compared with the general population, RA patients have an approximately twofold increase in lymphoma risk and greater risk of Hodgkins than non-Hodgkins lymphoma. There was also data to suggest an increased risk of lung cancer but a decreased risk for colorectal and breast cancer.

The prevalence of psychological distress among patients with rheumatic diseases is a well known and highly documented phenomenon. Among patients with SLE, there is evidence to suggest a range of 16–65% of patients in active disease states who meet criteria for a psychological disorder [41, 42]. In particular, mood and anxiety disorders appear to be the most frequently occurring [41, 43]. One study showed that 69% of patients diagnosed with SLE were positive for a lifetime history of mood disorder and 52% for lifetime anxiety disorder [44]. Some research links psychological distress, particularly depression, with disease activity in SLE. Segui et al. evaluated patients for depression and anxiety during both active and inactive stages of their disease [42]. Forty percent of participants were diagnosed with a psychological disorder during the acute phase, but only 10% met criteria a year later when the participants no longer displayed disease activity associated with SLE. However, it is often difficult to determine whether this phenomenon has biological influences or is a psychological adaptation to managing a chronic illness. In a study comparing depressive symptoms in patients with RA and patients diagnosed with osteoarthritis (a chronic non-inflammatory degenerative disease), those with the inflammatory disease were found to have significantly higher depressive symptoms [45]. The authors point out that while the two diseases are similar in terms of pain and functional impairments, the difference may be the neuroimmunobiological cytokine mechanism in inflammatory diseases, postulated to play a role in the development of depression. Psychological distress is associated with increased inflammation in both healthy individuals and RA patients [23, 46]. Depression could facilitate the development of inflammation by leading to poor health behaviors, hormonal dysregulation, and vulnerability to atherogenesis [47, 48]. Depression has also been specifically linked to increased levels of CRP and IL-6, as well as increased weight, which itself has been associated with the release of pro-inflammatory cytokines [49, 50].

While results suggest that some depressive symptoms are correlated with CRP and other biomarkers of inflammation, particularly among women with RA, the relationship may be at least partially explained by disease-related factors, such as increased pain among patients with higher levels of inflammation [51]. The proposition that inflammation leads to depression among RA patients may deserve closer evaluation in longitudinal studies. In addition to experiencing increased pain, patients with RA and SLE often have symptoms such as fatigue and sleep disturbance that may mimic or interact with depression. Results have indicated that depression is a stronger contributor to patient fatigue than self-reported disease activity [52]. Moreover, depression in patients with inflammatory disease predictor of mortality, affects quality of life, increases healthcare costs and contributes to disability [53].