Journal of Evidence-Based Complementary & Alternative Medicine
2017, Vol. 22(3) 502-512

DOI: 10.1177/2156587216676122
journals.sagepub.com/home/cam
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Cancer and Cancer-Related Fatigue and the Interrelationships With Depression, Stress, and Inflammation

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Abstract

Cancer-related fatigue (CRF) is a common symptom experienced in cancer patients. Depression, anxiety, and stress are associated with cancer. Depression and anxiety are also associated with CRF. At the cellular level, much is known about the impact of stress on the body generally, and its potential role in cancer. Stress, anxiety, and depression have been found to depress the immune system. Depression and stress have also been found to create inflammatory changes in the body and there is emerging evidence that inflammation is involved in cancer pathogenesis and in CRF. This article examines the relationships between stress, anxiety, depression, and cancer; relationships between anxiety and depression and CRF; and what happens at the cellular level, including impact on the immune system and emerging evidence of the role of inflammation in CRF. It also reports on research in relation to some Chinese herbal medicines that may be used to treat CRF.

Keywords

Chinese herbs, cancer-related fatigue

Received March 23, 2016. Received revised August 16, 2016. Accepted for publication October 2, 2016.

Cancer-related fatigue (CRF) is one of the most prevalent symptoms patients with cancer experience, both during and after treatment and in disease-free survivors. It has a significant impact on the quality of life and CRF is pervasive. CRF is defined as a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning.[1] Fatigue is the most common cancer symptom and was reported by 66% of patients.[2] CRF has been found to be experienced by 40% of patients at diagnosis and up to 90% of patients treated with radiation and nearly 100% of those treated with chemotherapy and may last years after cessation of treatment.[3] Management strategies include the use of psychoeducational interventions, exercise programs, and pharmacological treatments.[4]

The complexity of CRF as a concept and the variability in the method of CRF assessment pose a challenge to investigators attempting to understand the etiology of CRF. The term CRF has been used to describe both an objective physical or mental deficit in performance as well as a subjective mental state.[4] Although subjective fatigue is often related to objective changes in physical functioning or impaired performance status, the 2 phenomena are not synonymous and need to be distinguished. It is possible to perform poorly on tests of physical functioning yet not complain of fatigue, or the opposite.[4] Difficulties interpreting self-evaluations of CRF is that there is a need to take account of the background level of fatigue in the general population.[4] Establishing a clear definition of a phenomenon, such as CRF, is an essential starting point for phenotypic characterization and biomarker discovery.[5] There is a need for a better definition and clearer phenotypic characterization of CRF.[6] There are several robust and reliable assessment instruments to measure fatigue severity, and criteria for CRF syndrome have been proposed. One example is the assessment questionnaire *FACIT-F: Functional Assessment of Chronic Illness Therapy–Fatigue*, which is available from http://www.facit.org/FACITOrg/Questionnaires (www.facit.org). Another is the *Cancer Fatigue Scale*.[7]

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CRF occurs regardless of race, cancer type, stage, or treatment and can have severe physical, mental, economic, and social consequences.[3]

There is evidence that depression and anxiety is associated with cancer and CRF. Stress is also known to be associated with cancer. Increasingly, evidence is mounting of the role of inflammation, known to be involved in cancer pathogenesis,[8] in CRF.

This article will first examine the evidence of associations between depression, anxiety, and cancer, and between stress and cancer (risks and outcomes), to understand at a meta-level what relationships might exist. We will then examine the relationship between depression, anxiety, and CRF. We then move to the level of cells to examine some of the pathomechanisms that occur as a result of stress and depression and how these may be involved in cancer. We examine the pathomechanisms that may underpin CRF, including emerging evidence of the role of inflammation in CRF. Finally, we take a short look at some of the evidence of the efficacy of Chinese herbs in the treatment of CRF.

Relationships Between Depression, Anxiety, and Cancer

Depression and Anxiety in Cancer

Depression is a comorbid, disabling syndrome that affects approximately 15% to 25% of cancer patients.[9,10] In a study by Linden et al,[11] 12.9% of patients reported clinical symptoms of depression and an additional 16.5% described subclinical symptoms, and 19% showed clinical levels of anxiety with another 22.6% having subclinical symptoms. There was a gender difference found: Women showed higher rates of anxiety and depression, and for some cancer types, the prevalence was 2 to 3 times higher than that seen for men. In some cancer types, emotional distress was inversely related to age. They also found differences in distress level with different forms of cancer: Analyses by cancer type revealed significant differences such that patients with lung, gynecological, or hematological cancer reported the highest levels of distress at the time point of cancer diagnosis.

A meta-analysis of 58 studies conducted from 1980 to 1994 demonstrated that cancer patients were significantly more depressed than the normal population and that there were significant differences among groups with regard to sex, age, and type of cancer.[12] Another review of 49 studies of depression in cancer patients revealed no gender differences, although the prevalence of depression in women was found to be greater than the prevalence in men,[13] consistent with what Linden et al[11] found.

According to Spiegel and Giese-Davis,[14] depression prevalence in cancer patients increases with disease severity and symptoms such as pain and fatigue. They report that while the evidence of depression as a predictor of cancer incidence is equivocal, chronic and severe depression may be associated with elevated cancer risk. The evidence is stronger (albeit the literature still divided) that depression predicts cancer progression and mortality; however, this is complicated by several factors including the fact that some symptoms of cancer and cancer treatment may mimic depression, and disease progression can have a detrimental effect on mood.[14]

Studies show that half of all cancer patients have a psychiatric disorder, usually an adjustment disorder with depression. Effective psychotherapeutic treatment for depression has been found to affect the course of cancer. Psychotherapy for medically ill cancer patients has reduced anxiety and depression, and often pain. In 3 randomized studies reported previously by Spiegel et al,[15] psychotherapy resulted in longer survival time for patients with breast cancer (18 months), lymphoma, and malignant melanoma compared with controls. The treatment of depression in cancer patients may be considered a part of medical as well as psychiatric treatment.[16]

Difficulties Investigating Relationship Between Depression and Cancer

Depression has been challenging to study because symptoms occur on a spectrum that ranges from sadness to major affective disorder, and mood change is often difficult to evaluate when a patient is confronted by repeated threats to life, is receiving cancer treatments, is fatigued, and/or is experiencing pain.[17] In early, usually cross-sectional studies, the rate of depression was usually reported for adults with all types and stages of cancer. Depression was reported by severity (borderline, mild, moderate, severe), by a symptom such as depressed mood, or by some of these diagnostic categories: major depression, minor depression, depressive disorder, adjustment disorder with depressed mood, or dysthymia.[18] Most research groups reported the gender and age (usually older) of study subjects, but findings often were not reported by demographic variables. Racial and cultural minorities were always underrepresented in these studies.[19]

Associations Between Stress, Cancer Risk, and Cancer Outcomes

There is some evidence of an association between stress, incidence of cancer, and cancer outcomes. There is also some research to suggest personality characteristics and major life events may be important. However, before we examine some of the research findings, we need to understand "stress."

What Is Stress?

Hans Selye (1907-1982), a Canadian endocrinologist, was perhaps the first to demonstrate the existence of biological stress and its impact on health. Selye discovered and documented that stress differs from other physical responses in that stress is stressful whether one receives good or bad news, whether the impulse is positive or negative. He called negative stress "distress" and positive stress "eustress."[20] Activation of the stress system leads to behavioral and peripheral changes, including immunity.[21]

A current yet simple definition is stress is a condition where an environmental demand exceeds the natural regulatory

capacity of an organism to manage.[22] Results of a study by Stępka and Basińska[23] indicated the relationship between fatigue and emotionality in a statistical analysis. They showed a negative correlation between the nature of emotional components, distress, fear, anger, and the general rate of fatigue. Stress, in addition to being itself, is also the cause of itself, and the result of itself.[24]

Association Between Stress and Cancer Incidence and Outcomes

The link between stress and cancer is complex. There is a possible link between the chronic stress response, which may predispose patients to depression, and the risk of mortality from cancer.[25] A diagnosis of cancer and the typical treatment regimes and uncertainty associated with cancer are, naturally, very stressful psychologically and this has an effect on the soma or body. How well a person can adjust psychologically may determine how they fare in the longer term. However, prediagnosis, whether stress can contribute to the development of cancer in the first place is an important question.

A substantial body of research has investigated the associations between stress-related psychosocial factors and cancer development and outcomes. Chida et al[26] reviewed 165 studies and results indicate that stress-related psychosocial factors are associated with higher cancer incidence in initially healthy populations ($P = .005$); in addition, poorer survival in patients with diagnosed cancer was noted in 330 studies ($P < .001$), and higher cancer mortality was seen in 53 studies ($P < .001$). Stress-prone personality or unfavorable coping styles and negative emotional responses or poor quality of life were related to higher cancer incidence, poorer cancer survival, and higher cancer mortality. Site-specific analyses indicate that psychosocial factors are associated with a higher incidence of lung cancer and poorer survival in patients with breast, lung, head and neck, hepatobiliary, and lymphoid or hematopoietic cancers.

Personality Variables and Cancer Outcomes and Adjustment

Personality variables were much more predictive of death from cancer or cardiovascular disease than was smoking, and that different personality types were susceptible to either of these 2 diseases. Personality types were defined in terms of differential ways of dealing with interpersonal stress, and it was found that stress was a very potent cause of death, in the sense that stressed probands had a 40% higher death rate than nonstressed probands.[27]

Personality traits have also been associated with positive and negative adjustment to a cancer diagnosis. Overdependence scores were positively and significantly correlated with patients' anxiety and negatively and significantly correlated with the physician-patient relationship. Detachment scores were positively and significantly correlated with pain, somatization, depression, and anxiety and marginally associated with lower health-related quality of life. These preliminary findings support the construct validity and clinical utility of trait dependency and detachment testing with oncology patients and suggest that detachment is associated with poorer quality of life and higher psychological distress, whereas dependency is associated with poorer doctor-patient relationships after a cancer diagnosis.[28]

Major Life Events and Risk of Cancer

The literature is still divided on whether major life events are associated with an increased risk of cancer. For example, a Finnish prospective study of 10 808 women (from the Finnish Twin Cohort) found an association between the accumulation of life events during the 5 years prior to baseline assessment and an increased risk of breast cancer during the ensuing 15 years of follow-up. Independently, divorce/separation, death of a husband, and death of a close relative or friend were all associated with increased risk of breast cancer.[29] In contrast, other studies in the United Kingdom, Scandinavia, and Israel did not find an increased risk of breast cancer in relation to other single life events, including death of a spouse, divorce, or death of a child.[29] Some case-control studies have also found an increased risk of breast cancer in those women reporting a high total number of self-reported life events and/or one or more major life events 2 to 10 years prior to cancer diagnosis, while other studies have not found evidence of an association.[29]

A Turkish study found that 41.7% of cancer patients had at least 1 type of stress in the year prior to diagnosis though this study had no control group so conclusions are limited.[30] A meta-analysis of 15 studies investigating the role of stress in breast cancer initiation found that those with cancer reported adverse life events twice as often as controls; however, the majority of studies suffered from poor research methodology and when only studies of high quality (5 studies) were considered, there was no significant difference between cancer patients and controls.[31] An observational cohort study of stressful life experiences failed to show an increased risk of breast cancer relapse.[32] With respect to cancer progression, Dalton et al[33] found that 7 of 8 comparison studies in breast cancer did not support the contention that stressful events were associated with cancer progression.

Avoidance Symptoms

A study by Butler et al[34] indicated that a sizable proportion of women experienced clinically significant levels of intrusion and avoidance symptoms related to their cancer, particularly those with both more stressful past life events and higher current levels of aversive emotional support. Their symptoms were associated with shorter time since recurrence, and avoidance symptoms were associated with smaller emotional support networks. These results indicate that metastatic breast cancer is an emotionally traumatic event for a significant proportion of women, particularly those with past life stressors and unsupportive social environments.

Association Between Depression, Anxiety, and Cancer-Related Fatigue

Factors that have been found, using conceptual models of fatigue, to correlate with CRF include symptom distress (eg, pain, nausea/vomiting, dyspnea, lack of appetite) and psychological distress (eg, anxiety and depression). Higher levels of symptom and psychological distress seem to be associated with higher levels of CRF.[3]

A meta-analysis by Seo et al[35] found that both depression and anxiety were significantly associated with CRF and that the correlation of anxiety (mean effect size 1.11) was much lower than that of depression (mean effect size 1.49). They also found that a higher level of anxiety and depression were both associated with a higher level of CRF, and that psychological distress (anxiety and depression) was more strongly correlated with CRF than symptom distress.

Another study in breast cancer survivors found an association between fatigue and level of depression and other factors. Approximately one-third of breast cancer survivors assessed reported more severe fatigue, which was associated with significantly higher levels of depression, pain, and sleep disturbance. In addition, fatigued women with cancer were more bothered by menopausal symptoms and were somewhat more likely to have received chemotherapy (with or without radiation therapy) than nonfatigued women. In multivariate analyses, depression and pain emerged as the strongest predictors of fatigue.[36]

Teasing Out the Relationship Between CRF and Potentially Associated Factors

Some studies have attempted to tease out the relationship between CRF and factors including stress, anxiety, pain severity, sleep quality and depression. The relationship between stress and illness is complex. The susceptibility to stress varies from person to person. Among the factors that influenced the susceptibility to stress are genetic vulnerability, coping style, type of personality, and social support.[37] Results of various research studies indicate that interplay between CRF and these various factors that can accompany cancer are somewhat complex and not straightforward. Consideration of the complex causal mechanisms goes some way to explaining why it remains difficult to distinguish between fatigue and depression. In addition to fatigue being a possible cause of depression and depression being a possible cause of fatigue, both fatigue and depression can share a common cause. That is, certain forms of cancer and cancer treatment can cause both fatigue and depression.[38]

One cross-sectional study of 133 Chinese women with early-stage breast cancer, the majority of who had completed surgery and chemotherapy and were awaiting radiation treatment, found that 45% were severely fatigued, interfering moderately with daily functioning. Their mean perceived stress score was significantly higher than that of local healthy women and US breast cancer patients. Perceived stress, anxiety, and pain severity were found to be significantly associated with CRF, but depression and sleep quality were not. In addition, higher perceived stress, higher anxiety, and higher pain severity were associated with greater severity of CRF. The association of CRF with perceived stress was partially mediated by anxiety, which the authors believe might suggest a potential pathway from cancer and cancer treatment to CRF.[39]

Their results were in contrast to a study that found that the correlation between CRF was stronger for depression than anxiety.[40] However, their results are consistent with other studies have found cancer patients experience higher anxiety and lower depression at diagnosis, but lower anxiety and higher depression following treatment, and that somatic complaints of fatigue at diagnosis have been found to predominantly relate to anxiety symptoms. It is not possible, however, to make causal inferences from this study since it is cross-sectional in nature.[39]

A study was conducted by Okuyama et al[41] to investigate the potential correlation factors in fatigue in disease-free breast cancer patients. A group of 134 randomly selected ambulatory breast cancer patients who had undergone successful surgical treatment participated. They completed the *Cancer Fatigue Scale*, the *Hospital Anxiety and Depression Scale*, the *Mental Adjustment to Cancer Scale*, and an ad hoc questionnaire detailing physical symptoms, social support, and demographic variables at home and returned them by mail the following day. Their results suggest that fatigue in this population is determined by current physical and psychological distress rather than by the cancer itself and prior cancer treatments, and that the management of dyspnea, insomnia, and depression might be important in reducing fatigue in this population.

While more studies are clearly needed to elucidate the relationships between CRF and various factors, one needs to keep in mind that in combining the results for groups of people in quantitative studies, what is lost is the information about individuals. In addition to quantitative studies, more qualitative research would be very valuable as a means of investigating the impact and interrelationship between CRF and some of these coexisting factors.

In the next part of the article, we will look at what is happening at the cellular level, in particular how stress and depression may impact, then move on to discuss what is understood with regard to the underlying pathogenesis of CRF.

The Cellular Level: Impact of Stress and Depression

In this section, we will first look at the impact of stress on health more broadly, as this provides some important background, and from there, we will look at the impact of stress, depression, and anxiety on the body at the cellular level.

Stress and Its Impact on Health

It has been known for several decades that stress, whether inflammatory, traumatic, or psychological, is associated with

concurrent activation of the hypothalamic-pituitary-adrenal (HPA) axis. In the early 1990s, it also became apparent that cytokines and other humoral mediators of inflammation are potent activators of the central stress response, constituting the afferent limb of a feedback loop through which the immune/inflammatory system and the central nervous system communicate.[42] All 3 inflammatory cytokines, tumor necrosis factor–alpha (TNF-α), interleukin-1β (IL-1β), and IL-6 can cause stimulation of the HPA axis alone, or in synergy with each other.[43] There is evidence to suggest that IL-6, the main endocrine cytokine, plays the major role in the immune stimulation of the axis, especially in chronic inflammatory stress.[21]

The other major neural pathway activated by stress is the sympathetic nervous system. Stress mediators from the sympathetic nervous system may be able to directly modulate the growth and behavior of tumor cells quite separately from effects on the immune system.[30] Activation of the sympathetic nervous system is associated with the release of norepinephrine throughout the brain and in peripheral tissues, and stress experiments have demonstrated that plasma norepinephrine concentration is inversely related to particular immune functions of lymphocytes and monocytes.[30] Cytokine release is also affected by psychological stress.[30] Other changes at the cellular level have been discussed in the previous section on depression.

The persistent activation of the HPA axis in the chronic stress response and in depression probably impairs the immune response and contributes to the development and progression of some types of cancer. In general, both stressors and depression are associated with the decreased cytotoxic T-cell and natural killer (NK)-cell activities that affect processes such as immune surveillance of tumors, and with the events that modulate development and accumulation of somatic mutations and genomic instability.[44] This will be discussed in more detail in the next sections.

Stress and Cellular Immunity: Role in Cancer Pathogenesis

Research in animals and humans implicates stress (as well as depression) as playing a role in the initiation and progression of some types of cancer via impairment of the immune system.[31] Animal research indicates that stress has a negative impact on components of the immune system and is associated with increased mortality, growth, and metastasis of tumors in several animal tumor/cancer model studies.[44] The impact of social isolation, for example, has been investigated in mice: Researchers found that social isolation stress decreased the NK-cell activity and enhanced liver metastasis of colon carcinoma cells.[45]

Animal and human studies indicate that chronic stress can cause the release of particular mediators via HPA activation, which can suppress some nonspecific and specific parts of the immune response. This includes NK-cell activity, production of inflammatory cytokines, phagocytosis, and cytotoxic T-cell activity that are all involved in the immune response against tumors. Research also indicates that stress may negatively affect other biological processes, for example, leading to DNA damage, accumulation of somatic mutations, altered DNA repair and inhibition of apoptosis.[44] Such alterations of biological processes are known to be pathological mechanisms involved in some cancers.[8]

Data from infrahuman experiments have revealed that aversive insults may potentiate or inhibit tumorigenicity. Exacerbation of tumor growth is evident following acute exposure to uncontrollable but not controllable stress, and the effects of aversive stimuli vary as a function of prior stress history and social housing conditions. The fact that stress influences neurochemical, hormonal, and immunological functioning and that these changes are subject to many of the same manipulations that influence the carcinogenic process suggests a relation between these three mechanisms and the stress-induced alterations of tumor growth.[46]

A relatively recent study[47] found some evidence of a link between prior stressful experiences in childhood, evidence of decreased cellular immunity and cancer. Breast cancer survivors who experienced more childhood adversities had higher Epstein-Barr virus and cytomegalovirus antibody titers than those with fewer childhood adversities. The association between the elevated titers and childhood adversities remained after factoring in other potential factors such as health behaviors, markers of socioeconomic status, and depressive symptoms. Elevated Epstein-Barr virus and cytomegalovirus antibody titers (evidencing a reactivation of the viruses) reflect poorer cellular immune system control of the latent virus. Those who experienced more childhood adversities also had more depressive symptoms, less education, and poorer sleep quality than those with fewer childhood adversities.

Epstein-Barr virus and cytomegalovirus antibody titers were higher in women more recently treated for breast cancer than those who were treated less recently, and this may be due to the fact that cancer treatment can decrease cellular immunity.[47] The reactivation of herpes viruses, although typically asymptomatic and benign, is significant however, as elevated antibody titers can promote increases in inflammatory biomarkers such as TNF-α, IL-6, and C-reactive protein.[47] Inflammation, as detailed in a later section, is involved in cancer pathogenesis[8] (as well as the pathogenesis of a host of other chronic diseases), and has been implicated in the pathogenesis of CRF too (see later section). These findings add to the emerging literature suggesting that adverse early experiences may make people more vulnerable to immune dysregulation in adulthood. The consequences of early adversity appear to persist across the life span.[47]

Depression and Immune Function in Cancer

Depression affects components of immune function that may affect cancer surveillance. For example, stress and depression are associated with decreased cytotoxic T-cell and NK-cell activities which are involved in immune surveillance of tumors.[44] Lysis of a broad range of tumor cells is a key function

of NK cells.[30] Stress and depression are also associated with events that modulate development and accumulation of somatic mutations and genomic instability.[44]

It is also known that depressed and stressed patients have been found to have

> an overall leukocytosis, mild reduction in absolute NK-cell counts and relative T-cell proportions, marginal increases in the ratio of CD4 to CD8, higher concentrations of circulating neutrophils, reduced mitogen-stimulated lymphocyte proliferation and neutrophil phagocytosis, moderate decreases in T-cell and NK-cell functions, and reduced and changed monocyte activity.[44(p621)]

At the molecular level, patients with depression have been found to have higher serum and plasma levels of basal cortisol, complement components C3 and C4, specific antibodies against herpes simplex virus 1 and Epstein-Barr virus, and acute-phase proteins than in healthy controls.[44] Reiche et al[44] report that there is also evidence that concentrations of pro-inflammatory cytokine release is correlated with disease severity and HPA activity in patients with major depression (plasma concentration of and in vitro production of IL-1, IL-6, soluble IL-2, and IL-6 receptors were increased in depressed patients) though they caution that measurement of plasma concentrations of cytokines is not very reliable and that in vitro cytokine secretion provides more useful information.

Depression and Inflammation

According to Almond,[48] depression is frequently comorbid with many inflammatory illnesses, and increased inflammatory biomarkers are associated with major depressive disorder. Exposure to immune-modulating agents may increase the risk of developing depression.

Stress can activate pro-inflammatory pathways and inhibition of inflammatory pathways can improve mood.[48] This finding is very important and serves to underpin what might be seen, at the very least, as the interdependence of mind and soma if these are still to be conceptualized as separate entities. For those who espouse other models of the human, for example, Chinese medicine or ayurvedic medicine, the distinction between mind and body, of course is not separate in the Cartesian sense.

Anxiety and Poor Immunity

There is some evidence of an association between poor immunity and anxiety. For example, there is an association between latent herpes virus reactivation and attachment anxiety. Because elevated herpes virus antibody titers reflect poorer cellular immune system control over the latent virus, these data suggest that high attachment anxiety is associated with cellular immune dysregulation.[49]

In a study by Jaremka et al,[50] married couples (n = 85) provided saliva samples over 3 days and blood samples on 2 occasions. Participants with higher attachment anxiety produced more cortisol and had fewer numbers of CD3+ T cells, CD45+ T cells, CD3+CD4+ helper T cells, and CD3+CD8+ cytotoxic T cells than participants with lower attachment anxiety. Higher cortisol levels were also related to fewer numbers of CD3+, CD45+, CD3+CD4+, and CD3+CD8+ cells, which is consistent with research showing that cortisol alters the cellular immune response. This study also extends attachment theory in an important new direction by demonstrating the utility of a psychoneuroimmunological approach to the study of attachment anxiety, stress, and health. Attachment insecurity contributes to disease risk through a range of mechanisms, which include (1) disturbances in arousal and recovery within physiological systems that respond to stress; (2) physiological links between the mediators of social relationships, stress, and immunity; (3) links between relationship style and various health behaviors; and (4) disease risk factors that serve as external regulators of dysphoric affect, such as nicotine and alcohol.[51]

Underlying Mechanisms and Pathophysiology of CRF

The underlying mechanisms and pathophysiology of CRF are unclear, apart from chemotherapy-induced anaemia,[52] as are the relative contributions of the neoplastic disease, various forms of cancer therapy, and comorbid conditions (eg, anemia, cachexia, sleep disorders, depression). Several factors can influence CRF, including medical conditions, biochemical and psychological factors, and psychological factors such as depression and anxiety.[52] There is also evidence of a link between stress and CRF, discussed earlier. Stress is known to effect complex changes in biological pathways.

In any individual, the etiology of CRF probably involves the dysregulation of several physiological and biochemical systems. Mechanisms proposed as underlying CRF include serotonin (5-hydroxy tryptophan or 5-HT), dysregulation, vagal afferent activation and alterations in muscle and adenosine triphosphate metabolism (related to symptoms of physical fatigue, which may involve neuroactive agents such as serotonin, cytokines, and prostaglandins), HPA axis dysfunction (involving a range of neurotransmitters and hormones, including serotonin, cortisol, and testosterone), circadian rhythm disruption (disruption of the normal functioning of the suprachiasmic nucleus involving cortisol, serotonin, and various cytokines, resulting in disruption to sleep patterns and quality), and cytokine dysregulation.[53,54] Mental fatigue may be related to activity in the basal ganglia, cerebellum, and suprachiasmic nucleus.[54] Growth factors, specifically vascular endothelial growth factor have also been posited as playing a potential role in treatment-induced CRF.[55]

Pro-inflammatory cytokines such as IL-1, IL-6, and TNF-α are found in the tumor microenvironment and stress can induce glia cells within the central nervous system also produce cytokines in response. These cytokines are thought to contribute to CRF through their involvement in the pathogenesis of anemia, cachexia, anorexia, and depression, as well as by directly

influencing the HPA axis.[54] Stress is known to affect cortisol levels. Cortisol and serotonin both influence the functioning of the suprachiasmic nucleus involved in the regulation of the 24-hour circadian rhythm.[54] Bower et al[56] found that breast cancer survivors with CRF have a more flattened cortisol slope during the day and higher cortisol levels late evening compared with breast cancer survivors without CRF.

Potential Mechanisms Underpinning CRF Following Chemotherapy

A relatively recent 2011 study[57] has elucidated potential mechanisms underpinning CRF following chemotherapy. Fatigue, depression, and sleep disturbance are common adverse effects of cancer treatment and frequently co-occur. In this study, 103 women who had recently finished primary treatment (ie, surgery, radiation, chemotherapy) for early-stage breast cancer completed self-report scales and provided blood samples for determination of plasma levels of inflammatory markers: soluble TNF receptor II (sTNF-RII), IL-1 receptor antagonist, and C-reactive protein. Symptoms were elevated at the end of treatment; greater than 60% of participants reported clinically significant problems with fatigue and sleep, and 25% reported elevated depressive symptoms. Women treated with chemotherapy endorsed higher levels of all symptoms and also had higher plasma levels of sTNF-RII than women who did not receive chemotherapy.

This study confirms high rates of behavioral symptoms in breast cancer survivors, particularly those treated with chemotherapy, and indicates a role for TNF-α signaling as a contributor to postchemotherapy fatigue. Results also suggest that fatigue, sleep disturbance, and depression may stem from distinct biologic processes in posttreatment survivors, with inflammatory signaling contributing relatively specifically to fatigue.[57]

Inflammation, Cancer, and Cancer-Related Fatigue

The book *The Link Between Inflammation and Cancer: Wounds That Do Not Heal* explored the relationship between cancer and inflammation.[58] They state that nuclear factor–κB (NF-κB), a protein complex that controls transcription of DNA, cytokine production, and cell survival, has emerged as a major culprit in a variety of human cancers mainly because of its ability to protect transformed cells from apoptosis. These findings should not have come as a surprise since there exists a link between inflammation and many types of cancer, which was already suggested by Galen and later demonstrated by Virchow. Because NF-κB controls many genes involved in inflammation, it is not surprising that NF-κB is found to be chronically active in many inflammatory diseases such as cancer. NF-κB activation has also been observed in many solid tumors, but so far no oncogenic mutations responsible for NF-κB activation in carcinomas have been identified. In such cancers, NF-κB activation is a result of underlying inflammation or the consequence of formation of an inflammatory microenvironment during malignant progression. Most important, through its ability to upregulate the expression of tumor promoting cytokines, such as IL-6 or TNF-α, and survival genes, such as Bcl-X_L, NF-κB provides a critical link between inflammation and cancer.[59]

Rudolf Virchow (1821-1902) was the first to correctly link the origin of cancers from otherwise normal cells.[60] In 1855, he suggested that cancers arise from the activation of dormant cells (perhaps similar to cells now known as stem cells) present in mature tissue. Virchow believed that cancer is caused by severe irritation in the tissues, and his theory came to be known as "chronic irritation theory." It was only toward the end of the 20th century that Virchow's theory was taken seriously.[61] It was realized that specific cancers (including those of mesothelioma, lung, prostate, bladder, pancreatic, cervical, esophageal, melanoma, and head and neck) are indeed strongly associated with long-term inflammation.[62]

Emerging evidence suggests that inflammatory processes may be involved in CRF both during and after treatment. In a review by Bower et al,[63] the evidence for an association between inflammation and fatigue in cancer patients and survivors was studied. Furthermore, they identified potential mechanisms for persistent inflammation, focusing on the HPA axis. Guided by basic research on neuroimmune interactions, a growing body of research has examined the hypothesis that CRF is driven by activation of the pro-inflammatory cytokine network. A review by Bower and Lamkin[64] examined the current state of the evidence linking inflammation and CRF, drawing from recent human research and from experimental animal models probing effects of cancer and cancer treatment on inflammation and fatigue. In addition, they consider 2 key questions that are currently driving research in this area: what are the neural mechanisms of fatigue, and what are the biological and psychological factors that influence the onset and/or persistence of inflammation and fatigue in cancer patients and survivors? Identification of the mechanisms driving CRF and associated risk factors will facilitate the development of targeted interventions for vulnerable patients.

Increased cytokine and neopterin levels may be responsible for CRF. Schubert et al[65] quantitatively reviewed empirical findings on this topic, focusing on studies not using immunotherapy. Eighteen studies (1037 participants) of moderately high methodological quality were located and statistically analyzed. Most studies measured more than one inflammatory marker, resulting in a total of 58 correlation estimates. In 31 of these, they had to impute a null correlation because results had been simply reported, as nonsignificant and no further statistical information was available. General analyses based on weighting according to sample size showed a significantly positive correlation between fatigue and circulating levels of inflammatory markers ($r = 0.11$, $P < .0001$). Analyses of individual inflammatory markers revealed significantly positive correlations between fatigue and IL-6 ($r = 0.12$, $P = .004$), fatigue and IL-1ra ($r = 0.24$, $P = .0005$), and fatigue and neopterin ($r = 0.22$, $P = .0001$). Fatigue did not correlate

significantly with IL-1β ($r = 0.05$, $P = .42$) or TNF-α ($r = 0.04$, $P = .34$). Given its preliminary nature due to the limited available data, this quantitative review showed a positive association between cancer-related fatigue and circulating levels of IL-6, IL-1ra, and neopterin. Future studies examining the relationship between cancer related fatigue and inflammation would benefit from multiple rather than single blood sampling and from repeated daily ratings of the multidimensional nature of fatigue.

Leukocyte subsets, plasma inflammatory markers, and ex vivo pro-inflammatory cytokine production were assessed in 50 fatigued and nonfatigued breast cancer survivors recruited ≥2 years after successful primary therapy.[66] Fatigued breast cancer survivors showed elevations in serum markers associated with pro-inflammatory cytokine activity an average of 5 years after diagnosis. Results suggest mechanisms through which enduring immune activation may occur, including alterations in cortisol and in lymphocyte subsets.[56] Fatigued breast cancer survivors were distinguished from nonfatigued survivors by increased ex vivo monocyte production of IL-6 and TNF-α following lipopolysaccharide stimulation, elevated plasma IL-1ra and soluble IL-6 receptor, decreased monocyte cell-surface IL-6R, and decreased frequencies of activated T lymphocytes and myeloid dendritic cells in peripheral blood. These results extend links between fatigue and inflammatory markers to show a functional alteration in pro-inflammatory cytokine response to lipopolysaccharide and define a prognostic biomarker of behavioral fatigue.[66]

Bower et al[63] focused on inflammatory responses to psychological stressors and their relationship to circulating glucocorticoids and cellular sensitivity to glucocorticoid inhibition in breast cancer survivors. Relative to nonfatigued control survivors, participants experiencing persistent fatigue showed significantly greater increases in lipopolysaccharide-stimulated production of IL-1β and IL-6 following the stressor (group × time interaction: $P < .05$). Fatigued participants did not show any difference in cellular sensitivity to cortisol inhibition of cytokine production, but they did show significantly less salivary cortisol increase in the aftermath of the stressor. Moreover, blunted cortisol responses were associated with significantly increased production of IL-6 in response to lipopolysaccharide stimulation ($P < .05$). These data provide further evidence of enhanced inflammatory processes in fatigued breast cancer survivors and suggest that these processes may stem in part from decreased glucocorticoid response to stress.

Research on the Efficacy of Chinese Herbal Medicines in the Treatment of Fatigue

Several Chinese herbal medicines (medicinal formulae consisting of several Chinese herbs in combination) have been investigated in relation to their efficacy in treating the side effects associated with orthodox cancer treatment, including CRF. What follows is a short summary of some of these only.

LCS101 Formula

(*Astragalus membranaceus* [huang qi], *Poriae cocos* [fu ling], *Atractylodes macrocephala* [bai zhu], *Lycium chinense* [gou qi zi], *Ligustrum lucidum* [nu zhen zi], *Paeonia lactiflora* [chi shao yao or bai shao], *Paeonia obovata* [mu dan], *Citrus reticulate* [chen pi], *Ophiopogon japonicas* [mai men dong], *Milletia reticulate* [ji xue teng], *Oldenlandia diffusa* [bai hua she she cao], *Scutellaria barbata* [ban zhi lian], *Prunella vulgaris* [xia ku cao], and *Glehnia littoralis* [sha shen]).

Samuels et al[67] treated a series of 20 female breast cancer patients with the herbal compound LCS101 as an adjuvant to conventional chemotherapy. Their results indicated that at the end of treatment, 70% reported that they had either no or mildly severe levels of fatigue; 60% had none to mildly severe weakness; 85% had none to mildly severe pain; 70% had none to mildly severe nausea; and 80% reported none to mildly severe vomiting. Results indicated that 20% reported severe impairment of overall function, and 40% severely impaired quality of life. Significantly, 85% reported that they believed the botanical compound helped reduce their symptoms. Results also indicated that no toxic side effects were attributed to the LCS101 treatment by the study participants.

Shenqi Fuzheng Injection

(Key herbs: *Codonopsis lanceolata* [dang shen] and *Astragalus membranaceus* [huang qi])

A study by Jiang et al[68] investigated the efficacy of Shenqi Fuzheng injection combined with chemotherapy compared with control treatment (chemotherapy alone) in 67 patients with advanced lung cancer. They found that the efficacy rate in the treatment group (57.1%) was significantly greater than the control (31.2%, $P = .05$). In the treatment group, symptoms of fatigue, anorexia, and nausea and vomiting were lower compared with the control group. Also, the occurrence of leukopenia and thrombocytopenia in the treatment group was lower than that of the control group. The authors concluded that Shenqi Fuzheng injection plus chemotherapy for advanced lung cancer can reduce drug toxicity, improve the patient's fatigue, loss of appetite, gastrointestinal symptoms and improve the quality of life of patients.

Kangai Injection

(Key herbs: *Astragalus membranaceus* [huang qi], ginseng [ren shen], oxymatrine; extracted from *Sophora flavescens* [ku shen])

A study by Wu and Yang[69] investigated the efficacy of Kangai injection plus chemotherapy versus control (chemotherapy) in 80 patients with advanced gastric cancer. They found that in the treatment group NK-cell activity and CD4/CD8 ratio was significantly higher after treatment, and CD3

and CD4 were increased ($P = .05$). There was no significant difference in the efficacy rate between the treatment group (45%) and the control group (40%). There was less leukopenia, nausea and/or vomiting, peripheral nerve toxicity, in the treatment group compared with the control group ($P = .05$), less fatigue, better appetite and Karnofsky score increased in the treatment group ($P < .01$). They also found that treatment was more effective in relieving pain and assisting patients to gain weight compared with the control medication ($P = .05$). The authors concluded that treatment of advanced gastric cancer with Kangai injection in conjunction with chemotherapy may reduce the negative impact of chemotherapy on the patient's immune function and reduce side effects, thereby improving quality of life.

Conclusion

This article has sought to examine some of the key research findings in relation to cancer, CRF, stress, depression, and anxiety. There is evidence of an association between depression, anxiety, cancer and CRF. Stress-related psychosocial factors, including stress-prone personality appear to be associated with a greater incidence of cancer, poorer survival, and higher mortality in cancer patients. The literature is somewhat divided on whether there is evidence of an association between stressful life events and increased risk of cancer, and many studies have suffered from methodological shortcomings.

What is happening at the cellular level is perhaps less contentious, albeit very complex. Stress, depression, and anxiety are associated with changes at the cellular level involving components and activities of the immune system. Stress has also been found to affect the sympathetic nervous system and cytokine release, and stress may have a direct effect on tumors as well as via the immune system. Inflammation, implicated in pathophysiology of cancer as well as other chronic diseases, appears to play a role in the pathophysiology of CRF. Many of the inflammatory mediators involved in CRF are those involved in the stress response, and this is perhaps not surprising. Cancer can perhaps be seen as a somatic representation of stress.

What underpins these associations at the cellular pathway level is important to understand as not only does it assist in understanding what is happening at the level of psyche and soma in cancer, but also may assist in developing and measuring efficacy of novel therapeutic targets and therapies, as well as preventing cancer in the first place.

Cancer is a complex disease with multiple etiologies and multiple expressions, of which fatigue is just one.

Author Contributions

Daniel Weber and Kylie O'Brien equally contributed to the paper.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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