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Biobehavioral Influences on Cancer Progression

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Synopsis

This review focuses on the contributions of stress-related behavioral factors to cancer growth and metastasis and the biobehavioral mechanisms underlying these relationships. We describe behavioral factors that are important in modulation of the stress response and the pivotal role of neuroendocrine regulation in the downstream alteration of physiological pathways relevant to cancer control, including the cellular immune response, inflammation, and tumor angiogenesis, invasion, and cell-signaling pathways. Consequences for cancer progression and metastasis, as well as quality of life, are delineated. Finally, behavioral and pharmacological interventions for cancer patients with the potential to alter these biobehavioral pathways are discussed.

Keywords

Cancer; stress; depression; immunity; inflammation; angiogenesis

Introduction

Epidemiologically documented risk factors for carcinogenesis, including genetic, endocrine, environmental, and socioeconomic factors only account for part of the risk for cancer initiation [1]. Similarly, cancer patients who have a similar prognosis based on known clinical risk factors vary significantly with respect to disease outcomes. Emerging research has focused on the contributions of behavioral factors and neuroendocrine stress response pathways in explaining this individual variation. This area of research stems from epidemiological and other observational studies showing links between factors such as life stress, depression, social support, and cancer. Evidence for the contribution of behavioral

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factors to cancer initiation is modest and findings are inconsistent [2–5], with the most promising work focusing on interactions between behavioral factors and other host factors that may confer vulnerability such as aging and tobacco use [6]. However, a much stronger literature supports links between behavioral factors and cancer progression once a tumor has been established [7–18]. This review, therefore, focuses on contributions of behavioral factors to disease progression and potential mechanisms underlying these relationships. We will describe behavioral factors that are important in modulation of the stress response and the pivotal role of neuroendocrine regulation in the downstream alteration of immune, inflammatory, and tumor physiology. Consequences for cancer growth and progression will be delineated, and implications of these findings for behavioral and pharmacological interventions will be discussed.

Biobehavioral Model of Cancer Control

Behavioral factors

Stress is commonly defined as the experience of a negative life event or the occurrence of such an event along with a subjective evaluation of inadequacy to effectively cope with it [19]. Diagnosis with a life-threatening illness such as cancer is almost universally experienced as stressful [20–22]. Additionally, cancer diagnosis and treatment are accompanied by a number of acute and chronic stressors that can impact quality of life. Severe life stress is often associated with the development of depression or anxiety [23–26]. Not surprisingly, depression is common among individuals with cancer, with about one-third of cancer patients reporting depressive symptoms at the time of diagnosis and up to one-fourth suffering from symptoms sufficient to meet criteria for a clinical diagnosis of major depression [27,28].

Whereas most behavioral research in cancer has focused on distress and negative emotions, there has been growing attention to markers of resilience [29]. Social support, frequently defined as the degree of perceived satisfaction with social relationships, is an important psychological resource. It is thought to have direct benefits for psychological and health outcomes and to buffer the effects of stress on mental and physical health [30–33]. High levels of social support have been consistently associated with diminished risk for morbidity and mortality, with statistical effect sizes comparable to those of standard health risk factors such as smoking, blood pressure, cholesterol, obesity, and exercise [34]. Additional resilience factors, including optimism and the ability to find meaning or perceive some benefit in one's experience with cancer, will also be discussed.

Although health practices such as diet, exercise, and tobacco use also fall within the realm of behavior, these influences have already been characterized in other literatures. The current review will focus on the roles of psychological and social factors in cancer progression. A model of biobehavioral processes relevant to cancer control is illustrated in Figure 1.

Neuroendocrine stress response pathways

External events evaluated as threatening or stressful activate cortical and limbic structures of the central nervous system and ultimately activate the hypothalamic pituitary adrenocortical (HPA) axis and sympathetic nervous system [35]. Specifically, corticotrophin-releasing hormone (CRH) and vasopressin are secreted from the paraventricular nucleus of the hypothalamus in response to psychological stress or other affective experiences. These neurohormones stimulate the anterior pituitary to produce adrenocorticotrophic hormone (ACTH), which in turn stimulates the release of the glucocorticoid hormone cortisol from the adrenal glands. The sympathetic nervous system (SNS) is known for its role in the “fight-or-flight” stress response. Sympathetic fibers innervate the adrenal medulla, releasing acetylcholine, which activates the secretion of epinephrine (E) and norepinephrine (NE).

SNS fibers also directly innervate many tissues, including primary and secondary lymphoid tissue where they are involved in the regulation of the immune response. Glucocorticoids, catecholamines, and other neuroendocrine factors have been shown to have modulatory effects on immune processes relevant to tumor surveillance and containment, as well as on other pathophysiological processes important in cancer progression, including angiogenesis, invasion, and modulation of inflammation [6,36–38]. These pathways and their translational implications will be discussed later.

Biobehavioral Pathways: Immunosuppression

Modulating effects of behavioral factors on the cellular immune response via activation of the HPA and SNS have been well-characterized [39–41], with mechanisms including direct sympathetic innervation of immune tissue, presence of glucocorticoid and beta-adrenergic receptors on mononuclear leukocytes, and neuroendocrine modification of lymphocyte trafficking [37,40,42,43]. Psychological stress and affective responses, including depression and anxiety, have been associated with downregulation of cellular immune responses, including the number and type of lymphocytes in circulation, proliferative and cytolytic responses *in vitro*, and antibody levels post-immunization [44,45]. These findings are thought to have relevance to cancer control because of the potential role of cellular immunity, particularly Natural Killer (NK) cell activity, in the defense against malignant cells [46,47]. The underlying assumption of the immunosuppression model is that stress or negative emotions can modulate tumor initiation and development by suppressing elements of the immune response important in responding to malignant cells [22,36,48–50].

Pre-clinical studies

Pre-clinical experimental studies have documented that chronic stress, as well as significant acute stress associated with surgery, promote tumor incidence and progression via suppression of NK and T cell activities, impairment of antigen presentation, and enhancement of T regulatory cells [51–54]. An extensive series of studies has demonstrated that that stress-induced release of catecholamines and prostaglandins, particularly in the peri-surgical period, suppress NK cell activity and other components of the cellular immune response, and this suppression can enhance tumor development and metastasis [52,53,55–57]. These findings have given rise to novel pharmacologic therapeutic strategies, which will be discussed below.

Clinical studies

Effects of behavioral factors on the immune response have been examined in early-stage breast cancer patients. One of the earliest clinical findings was that breast cancer patients with higher levels of perceived social support had greater NK cell activity than women who felt less supported. In contrast, those patients who reported more fatigue and depressive symptoms had lower NK cell activity [58–61]. The studies accounted for known prognostic factors, relationships between psychosocial factors and NK cell activity were found both shortly after breast cancer surgery and 3 months later, and findings were replicated in more than one patient sample. Psychosocial factors were also associated with time to recurrence; however, NK cell activity was not found to mediate the links between psychosocial factors and recurrence [62].

These findings have been extended in a more recent series of studies involving a large sample of breast cancer patients followed for 18 months post-surgery. After accounting for the relevant clinical factors, women who reported greater distress after surgery showed a diminished cellular immune response across a variety of measures including less robust NK cell activity, poorer response of NK cells to recombinant IFN γ , a decreased

lymphoproliferative response, and altered expression of inhibitory NK cell receptors [20,63]. Moreover, patients who displayed more rapid reductions in distress post-surgery also showed the fastest recovery of NK cell activity over time [64]. Other recent studies provide additional evidence for links between psychosocial factors and alteration of markers of cellular immunity, including NK cell count and activity, lymphoproliferative responses, and B and T cell subsets in breast cancer patients [e.g. 65,66–69] as well as among patients with other types of cancers, including gynecologic, prostate, gastrointestinal, digestive tract, and liver malignancies [70–74]. Whereas most research has focused on markers of stress and maladjustment and downregulation of cellular immunity, recent work has also attended to processes of resilience that may optimize immune function. For example, among women with early-stage breast cancer, a greater ability to find benefit in one's experience with cancer was associated with a better lymphoproliferative response [68]. Similarly, men with localized prostate cancer who were more optimistic and were able to more adaptively express their anger showed better NK cell cytotoxicity [72].

Despite the accumulating evidence the psychological state of cancer patients can alter cellular immunity, it should be noted that not all findings have been consistent [75], and effects on cellular immune markers have varied [64,67,76]. Moreover, the implications of these relationships for clinical endpoints including disease recurrence and survival have been difficult to investigate due to the large sample size and long follow-up required. A recent report showed that patients with hepatobiliary carcinoma who exceeded a cut-off score indicative of clinically significant depressive symptomatology showed lower NK cell numbers and shorter survival as compared to their non-depressed counterparts. Moreover, the authors found that NK cell count mediated the relationship between depression and survival [9].

There has been increasing attention to immune markers in the tumor microenvironment, where the potential for clinical significance may be greater. For example, studies of ovarian cancer patients examined cellular immune functioning in both peripheral blood and in tumor infiltrating lymphocytes (TIL). Distress was associated with poorer NK cell activity and lower TH₁/TH₂ cell ratios both in peripheral blood and in TIL. In contrast, social support was associated with greater NK cell activity in TIL and a greater percentage of NKT cells in tumor ascites [74,76,77].

The immunosuppression model has not been able to consistently account for links between behavioral factors and cancer outcomes, suggesting some limitations of this model in the biobehavioral context. It is important to consider that tumors have escape mechanisms by which they evade recognition and destruction by the immune response, including downregulation of Class I major histocompatibility complex (MHC-I) and tumor associated antigens, interference with costimulatory signals, and disruption of apoptotic signaling. Interactions of stress pathways with tumor escape mechanisms have been minimally investigated and may prove to be an area of great potential. In addition, it is now known that there are other mechanisms by which stress and psychological responses can influence the tumor microenvironment and the growth and progression of malignancies.

Biobehavioral Pathways: Angiogenesis, Invasion, and Cell Signaling

Malignant transformation, angiogenesis, and metastasis

Tumors are now understood to be complex tissues that are shaped by ongoing interactions between cancer cells and the surrounding microenvironment [78–80]. Many of the steps involved in malignant cell transformation and metastasis involve signaling interactions with surrounding cells that may be induced by tumor cells to secrete molecules supporting abnormal development, proliferation, and angiogenesis [81–83]. After the initial

transformation and proliferation, vascularization of the tumor mass is critical for its growth and metastatic spread [84,85]. This process, referred to as angiogenesis, is normally tightly controlled by positive and negative factors secreted by both tumor and host cells [85,86]. Pro-angiogenic molecules include vascular endothelial growth factor (VEGF), interleukin-6 (IL-6), and Interleukin 8 (IL-8). During tumor development, an “angiogenic switch” is triggered whereby the balance of angiogenic inducers and inhibitors changes, and angiogenesis proceeds [81]. After an adequate blood supply has been established, tumor cells invade the host tissues and the cancer grows locally [87]. The process of metastasis involves detachment and embolization of tumor cells, which travel through circulation and arrest in the capillary beds of specific organs and ultimately establish a new microenvironment at that site [87].

Stress-based modulation of angiogenesis

Increasing evidence has demonstrated that behavioral and neuroendocrine factors can modulate the tumor growth pathways described above [88–96]. *In vitro* studies have shown that tumor production of VEGF is stimulated by stress-related mediators such as norepinephrine (NE), epinephrine (E), and cortisol in ovarian cancer, melanoma, and nasopharyngeal cancer cell lines. This occurs via beta-adrenergic signaling and is blocked by the beta-blocker propranolol [93,94,97]. Pre-clinical experiments with an orthotopic model of ovarian cancer have demonstrated that chronic restraint stress increases tumor weight and number of tumor nodules. These effects were mediated by increases in VEGF and angiogenesis induced by beta-adrenergic pathways, could be replicated by the beta-adrenergic agonist isoproterenol, and were blocked by propranolol [91]. Similarly, surgical stress increased ovarian tumor growth in an orthotopic animal model via beta-adrenergically linked angiogenic pathways, with the stress effects reversed by beta adrenergic blockage [98]. Parallel findings have been observed in the clinical setting, where social isolation among women with ovarian cancer has been linked to higher levels of VEGF both in serum taken at the time of surgery and in tumor tissue [96,99].

Behavioral factors and stress response pathways can also modulate other cytokines involved in angiogenesis. Interleukin-6 (IL-6) is produced by tumor cells and tumor associated macrophages (TAM) and plays multiple roles in tumor progression, including a key role in angiogenesis [100,101]. IL-6 also stimulates proliferation of tumor cells [102,103], enhances tumor cell migration and attachment [103], promotes invasion of endothelial cells [104], and is associated with tumor progression and poorer clinical outcomes [105–107]. Of relevance to biobehavioral pathways, IL-6 is regulated by neural and endocrine stress responses via feedback loops with the HPA axis [108–110]. Moreover, IL-6 levels are elevated with sympathetic activation, acute and chronic stress, and depression [95,108,109,111–116]. Elevations of IL-6 in both plasma and ascites within the tumor compartment have been observed in ovarian cancer patients with greater social isolation, suggesting the potential clinical relevance of social interactions [117]. Interleukin-8 (IL-8) is another pro-angiogenic molecule induced by various stressors in humans [118,119]. *In vitro*, NE has been shown to stimulate IL-6 gene transcription through a Src-dependent mechanism and has increased IL-8 secretion in cancer cell lines, demonstrating effects of stress mechanisms on critical tumor signaling pathways [90,95,116].

In addition to activation of pro-angiogenic cytokines such as VEGF and IL-6, stress response pathways have been shown to directly activate angiogenesis-promoting molecules such as signal transducer and activator of transcription factor-3 (STAT-3). Stimulation by NE and E can activate STAT-3 independent of IL-6, leading to its downstream effects on cell proliferation, survival, and angiogenesis, as well as inhibition of apoptosis [120].

Invasion and migration

Stress hormones have also been shown to modulate migration and invasion of malignant cells by stimulating production of matrix metalloproteinases (MMP) by both tumor and stromal cells, and by serving as chemoattractants, inducing cell migration. For example, stimulation by NE and E significantly increased ovarian cancer cell production of MMP-2 and MMP-9 through the beta-adrenergic signaling pathway [89]. Similar enhancement of MMP production by catecholamines has also been reported in colon and head and neck cancers [94,121–123]. Both NE and cortisol have been shown to enhance MMP-9 production by human monocyte-derived macrophages *in vitro* [124]. Incubation with levels of NE commensurate with those that would be observed in the organ microenvironment during stress responses significantly increased the invasive potential of ovarian cancer cells, an effect that was reversed by the β -antagonist propranolol [89].

Recent findings have demonstrated that beta-adrenergic signaling promotes survival of ovarian cancer cells by inhibiting anoikis, the normal process of apoptosis that occurs when cells are separated from the extracellular matrix [92]. Resistance to anoikis is a key feature of malignant transformation and enhances the ability of tumor cells to migrate and metastasize to secondary sites. This process occurs through beta-adrenergic activation of focal adhesion kinase (FAK) and was seen both *in vitro* and in an orthotopic mouse model of ovarian cancer. In ovarian cancer patients, higher levels of pFAK^{Y397} were observed in patients with higher levels of depression or greater NE levels in their tumors. Furthermore, pFAK^{Y397} was linked to poorer overall survival [92]. These data indicate that stress-related FAK modulation may contribute to tumor progression.

Behavioral factors and gene regulation

Psychosocial profiles have also been linked to regulation of gene expression in ovarian cancer. Tumors from ovarian cancer patients with high levels of depression and low social support (high risk) were compared to those with low levels of depression and high social support (low risk) after being matched for age, grade, stage, and tumor histology. Genome-wide transcriptional analysis and promoter-based bioinformatics analyses were used for tumor profiling. Compared to low risk patients, tumors from high-risk patients showed over 200 upregulated gene transcripts and increased activity of signaling pathways involved in tumor growth and progression (e.g., CREB/ATF, NF κ B/Rel, STAT, and ETS-family transcription factors). High-risk patients also showed increased intratumoral NE levels [125]. These findings suggest that biobehavioral processes may regulate gene expression profiles within solid tumors. Beta-adrenergic transcription control pathways appear to be key candidates in mediation of these effects.

In sum, this emerging body of research provides compelling evidence that behavioral factors and stress response pathways are associated with key elements involved in tumor growth and development.

Biobehavioral Pathways: Inflammation

Inflammation and cancer: the role of macrophages

Inflammation is a common characteristic of epithelial tumors and serves as a tumor initiator and promoter [80]. Tumor associated macrophages (TAM) are a major contributor to inflammation and constitute a large proportion of most tumor microenvironments [126]. Drawn by tumor-derived chemotactic factors produced by tumors, peripheral monocytes are recruited to the tumor microenvironment, where they differentiate into macrophages. In the presence of a proinflammatory tumor microenvironment, macrophages are induced to switch from their phagocytic (M1) phenotype to an M2 phenotype that produces

immunosuppressive cytokines such as IL-10 and TGF β , key tumor-promoting molecules such as VEGF and MMPs, and some inflammatory cytokines [83,127,128]. TAM are thus directly involved in the following processes: 1) stimulation of angiogenesis, 2) stimulation of tumor proliferation, invasion, and metastases, 3) promotion of degradation and remodeling of the extracellular matrix, and 4) downregulation of the adaptive immune response [127,129–131]. It is therefore not surprising that extent of TAM infiltration is associated with poorer survival [132–134].

Biobehavioral and neuroendocrine modulation of inflammation

Links between distress, depression and inflammatory responses have been well-documented, with relationships thought to be mediated by HPA dysregulation [135,136]. Relationships between psychosocial factors and proinflammatory and pro-angiogenic cytokines have been observed in cancer patients, as reviewed earlier [96,99,117]. Inflammation in the tumor microenvironment is mediated by both tumor cells and immune cells such as macrophages. Behavioral factors such as stress and depression may contribute to enhanced tumor cell secretion of proinflammatory cytokines; for example, NE stimulates IL-6 expression by ovarian cancer cells [95]. Macrophages contain both alpha and beta-adrenergic receptors, and catecholamines have been shown to promote macrophage production of proinflammatory cytokines such as IL-1 β and TNF α , as well as MMP-9 [136–139]. Clinically, high levels of chronic stress, depression, and social isolation have been associated with TAM production of MMP-9 in ovarian cancer patients [124], suggesting that behavioral factors can alter the tumor microenvironment in a way that favors cancer progression. Behavioral factors have also been shown to affect transcriptional regulation of pathways relevant to inflammation and inflammatory control. For example, older adults with high levels of social isolation had profiles indicative of poorer control of inflammation, including impaired transcription of glucocorticoid response genes and increased activity of proinflammatory transcription control pathways in peripheral leukocytes [140]. Taken together, these findings indicate that macrophages and malignant cells are sensitive to neuroendocrine stress hormones in ways that may affect production of molecules that enhance tumor growth and decrease immune effectiveness.

Bidirectional Pathways: Effects of Inflammation on Depression and Quality of Life

The discussion thus far has focused on the role of behavioral factors in modulating inflammatory processes relevant to cancer control. However, it is also known that tumor- or treatment-induced peripheral proinflammatory cytokines can activate central nervous system pathways evoking a syndrome of behavioral and affective responses that have come to be called “sickness behaviors” as they mimic flu-like vegetative symptoms. There are several pathways mediating the effects of peripheral proinflammatory cytokines on the central nervous system, including passage through regions of permeability of the blood-brain barrier and stimulation of afferent fibers in the vagus nerve [141–144]. In the CNS, these pathways induce behavioral and affective symptoms such as depressed mood, fatigue, anorexia, impaired concentration, sleep disturbance, enhanced pain sensitivity, and reduced activity [142,144,145].

Although it has been commonly assumed that the high prevalence of depression among cancer patients is a reaction to the stress associated with a potentially life-threatening diagnosis and cancer treatment [146], it has also been hypothesized that inflammatory processes produced secondary to treatment or tumor growth may contribute to the pathogenesis of depression, as well as fatigue and debility in cancer patients [124,147,148]. Several studies have documented associations between elevated proinflammatory cytokines

and depression among cancer patients [124,147–150]. Similarly, a series of studies has shown that fatigued breast cancer survivors have higher levels of inflammatory markers such as serum Interleukin-1 receptor antagonist (IL-1ra), tumor necrosis factor receptor II (TNFRII), and neopterin, lower levels of serum cortisol, flatter diurnal cortisol slopes, and both enhanced inflammatory responses and blunted cortisol responses to an experimental psychological stressor [151–153]. Specific cytokine gene polymorphisms appear to underlie persistent fatigue in breast cancer patients such that patients demonstrating homozygosity for either variant of the IL-6 174 genotype or the presence of at least one cytosine at the IL-1 B-511 locus are more likely to be fatigued [154]. Cortisol dysregulation, particularly elevations in evening cortisol, has also been linked to fatigue and debility in ovarian cancer patients [150]. Taken together, these findings suggest that tumor- and treatment-derived proinflammatory cytokines, as well as inflammatory cytokine polymorphisms, contribute to a chronic state of inflammation, ultimately resulting in the emergence of “sickness behaviors” and dysregulation of the HPA axis [124].

Translational Implications: Behavioral and Pharmacologic Interventions

It is already known that behavioral interventions for cancer patients, including psychoeducational support groups and psychotherapy, can reduce anxiety, depression, and cancer-related distress and improve quality of life [155–158]. The evidence reviewed thus far also points to the potential for behavioral interventions that can reduce stress and mood disturbance to serve an adjunctive role to conventional treatments in improving outcomes for cancer patients. An early behavioral intervention trial found that women with metastatic breast cancer randomized to a year-long weekly support group survived an average of 18 months longer than women assigned to a control group [159,160]. However, there has been significant controversy over the meaning of the results [e.g. 161,162,163], and attempts to replicate in other samples of breast cancer patients have not been successful [164–169]. Results from studies of other behavioral interventions have also been mixed. While several trials have shown no survival effect [170–172], three randomized clinical trials have shown positive results [160,173–176]. One of the most striking findings was that an average of 7 hours of supportive psychotherapy improved survival among patients undergoing surgery for gastrointestinal malignancies, effects that were sustained at 2 and 10-year follow-ups [174,175].

Such findings have catalyzed interest in the potential mechanisms by which behavioral interventions could affect cancer outcomes. Most studies have focused on the roles of NK cell activity, lymphocyte proliferative response, and other markers cellular immune functioning. Indeed, there is evidence from a handful of large, well-designed randomized clinical trials that behavioral interventions that enhance social support and target stress management and other coping skills can improve neuroendocrine and cellular immune functioning.

For example, cognitive-behavioral stress management (CBSM) is a 10 session behavioral program conducted in a supportive group format and aims to assist patients in developing coping skills, utilizing social support, expressing emotions, and learning relaxation strategies. CBSM reduced anxiety and depression and appeared to normalize neuroendocrine functioning in breast cancer patients; women randomized to the intervention displayed a significant decline in cortisol over a 12-month follow-up period, while women in the control group did not show this decline [158,177–179]. CBSM participants also demonstrated better lymphoproliferative responses at a 3-month follow-up and better Th1 responses at a 6-month follow-up as indicated by greater Th1 cytokine production (IL-2 and IFN γ) and a higher IL-2 to IL-4 ratio; however, these differences were not sustained at a 12-month follow up [68,179]. The effect of CBSM on clinical outcomes has not yet been reported.

Another behavioral intervention that was provided in a supportive group format and targeted coping skills, stress management, health practices, and adherence to treatment demonstrated similar benefits for women with early-stage breast cancer in a randomized clinical trial. In addition to reducing distress and improving social support, the intervention also appeared to be protective with respect to immune functioning. T cell proliferative responses to phytohemagglutinin and concanavalin A remained stable or increased during the 4-month intervention period for participants randomized to the intervention while declining during the same time frame for women in the control group, an effect that was maintained at a 12-month follow-up [180,181]. Women who reported clinically significant depressive symptoms were especially likely to benefit; in addition to improvements in mood and quality of life, they also showed reductions in markers of inflammation (operationalized as white blood cell count, neutrophil count, and T helper to T suppressor cell ratio) [182]. Importantly, the intervention also improved clinical outcomes, including initial benefits in performance status, functional status, and overall health status [181]. Perhaps the most notable finding was that after a median of 11 years of follow up, women randomized to the psychological intervention showed a reduced risk of breast cancer recurrence and mortality [173]. The authors report plans to investigate whether improvements in cellular immune functioning or reduced inflammation in the intervention participants may be responsible for the survival differences.

A key component of these interventions appears to be the acquisition of specific skills to reduce the impact of stress both psychologically and physiologically. Mindfulness-Based Stress Reduction (MBSR) is an 8-week program that includes a number of such skills including mindfulness meditation, gentle yoga, and progressive muscle relaxation techniques. MBSR has shown promising effects in cancer patients including reduced distress, improved quality of life, declines in cortisol, enhanced NK cell functioning, and a quicker restoration of the balance of Th1 to Th2 cytokines to pre-treatment levels [183–186]. Other work has demonstrated benefits from brief training in relaxation techniques and guided imagery, including decreased cortisol; greater numbers of mature and activated T cells, NK cells, and lymphokine-activated killer subsets; improved NK cell activity; and enhanced lymphocyte proliferative responses [187–191].

Effects of psychosocial interventions on cellular immune functioning have not been found in all studies [e.g. 192,193,194], and the findings have not been uniformly positive in the studies reviewed above, with effects demonstrated for some parameters of immune functioning but not others. Nonetheless, there is compelling evidence from at least two large, randomized clinical trials for breast cancer patients that behavioral interventions can optimize cortisol regulation and cellular immune functioning. Follow-up work is needed to replicate and extend these findings, to examine effects of behavioral interventions on tumor growth pathways described above, and to determine whether the changes in physiology are of the type and magnitude necessary to alter clinical outcomes.

Targeting specific quality of life concerns, such as insomnia, is another promising avenue [145]. For example, a cognitive-behavioral intervention for chronic insomnia among early-stage breast cancer patients not only improved sleep and fatigue, but also increased $INF\gamma$ and $IL-1\beta$ from pre- to post-treatment, with $IL-1\beta$ changes maintained at a 1-year follow-up, effects the authors characterized as immune-enhancing. Lymphocyte counts also increased from post-treatment to later follow-up time points [195]. Interventions focusing on sleep further have the potential to modulate disease-induced alterations in circadian rhythms, which have been closely linked to neuroendocrine and immune regulation relevant to tumor growth [196,197].

Pharmacologic interventions that can modulate the stress response pathways described in this review also hold promise. There is already evidence that SSRIs can be effective in addressing cancer-related quality of life symptoms [198,199]. The role of antidepressants on tumor growth outcomes has been mixed, with both positive and negative effects reported, depending on the population and the antidepressant [200,201]. Based on evidence that stress-induced alterations in the tumor microenvironment appear to be mediated by beta-adrenergic signaling pathways, beta blockers have been proposed as a potential therapeutic strategy to attenuate these effects. Beta blockers have already been shown to reduce the effects of stress on suppression of NK cell activity and tumor development in animal models [202,203], and there is epidemiological evidence that beta blocker use reduces risk for the development of prostate cancer in humans [204]. Pilot clinical studies to examine the potential preventative effects of beta blockers are underway. Along similar lines, an innovative cocktail of catecholamine- and prostaglandin-blockers has been successfully used in an animal syngenic tumor model along with the immuno-stimulant poly-I-C to prevent peri-operative immunosuppression [205].

Future Directions: Sensitive Populations and Windows of Opportunity

The emerging body of literature provides compelling evidence that stress-related behavioral factors can modulate physiological pathways relevant to cancer control. As cancers are heterogeneous both in physiology and in treatment, it will be important to determine whether the biobehavioral relationships documented in breast and ovarian cancer patients are seen with other cancer sites and with varying disease burdens. For example, it has been proposed that hormonally-mediated malignancies, such as prostate and endometrial cancers, may follow similar patterns. Immune-mediated cancers, such as leukemias and lymphomas, also have the potential to be susceptible to the types of behavioral influences reviewed in this chapter [180].

Increased attention to clinical significance will be critical in translating findings to meaningful treatments and outcomes. It has been historically difficult to assess recurrence and survival because of the large sample sizes and long follow-up period required, but continued efforts in this direction are needed. Studies should also include other clinical endpoints relevant to morbidity and quality of life, as well as intermediate markers of disease processes. For example, the development of opportunistic infections following immunosuppressive therapy is an outcome that has relevance to quality of life, health care utilization, and survival. Other treatment complications such as neutropenia and pancytopenia can also greatly affect quality of life, may require additional intervention, and can delay therapy. Tumor markers used as an index of disease processes or response to treatment, such as CA125 in ovarian cancer, can easily be assessed even with a brief follow-up period.

We have previously recommended focusing on “windows of opportunity” in the disease and treatment trajectory which may be most sensitive to the effects of biobehavioral influences [6]. For example, behavioral factors may be most likely to influence immune functioning in a clinically significant way early in the development of the tumor as opposed to once the tumor is well-established and sophisticated tumor escape mechanisms have developed. The perioperative period has been proposed to be another critical time period due to the simultaneous occurrence of several risk factors for progression and metastasis, including increased angiogenesis, secretion of growth factors, shedding of tumor cells, and suppression of cellular immunity [55,203,206]. Following surgery, a small number of circulating cancer cells termed minimal residual disease (MRD) can remain and are thought to be the source of disease recurrence in some patients. Indices of cellular immune functioning, including leukocyte cytotoxicity and proliferative responses during this period,

predict better clinical outcomes [203,207,208]. Similarly, the recovery from immunosuppressive adjuvant treatment is likely to be another sensitive “window.” Following adjuvant therapy, MRD is also known to cause relapse, particularly for individuals with hematologic malignancies. The immune system must recover sufficiently to both recognize and destroy remaining malignant cells and to protect against secondary infections.

Hematopoietic stem cell transplantation

The setting of hematopoietic stem cell transplantation (HSCT) provides an illustrative example of some of these ideas. HSCT is a potentially curative but rigorous therapy with significant risk of morbidity and mortality. Patients with hematologic malignancies undergoing this treatment frequently experience physical and psychological sequelae that impair their quality of life and undermine recovery. Common adverse physical symptoms include nausea, fatigue, and mucositis as well as the serious complications of persistent infections [209,210]. In addition, 40–70% of patients relapse following autologous stem cell transplantation [211], and graft-versus-host disease is a common and potentially lethal complication of allogeneic transplantation and a cause of significant long-term disability. Thus, it is not surprising that many patients report significant emotional distress [212].

Depressed mood and low levels of hope prior to HSCT have predicted poorer survival post-transplant [213–216]. Biobehavioral pathways important to the control of hematologic malignancies and transplant complications could play a critical mediating role in this setting. As reviewed in this chapter, it is now widely accepted that many of the host- or recipient-derived cells essential to the recovery of hematopoiesis and immune competence also express receptors for the soluble and cellular factors that are responsive to the extensive crosstalk between psychological state and the neuroendocrine and immune systems. These interactions may be of particular significance for HSCT patients because any modulatory influence on immune processes could have a salient effect on relapse and survival. Immune reconstitution following transplant is directly associated with reduced relapse risk and overall and progression-free survival [211,217–219]. In addition to the potential effects on residual disease (MRD), recovery of immune competence is also critical for minimizing tissue damage and providing protection against bacterial and viral pathogens [219].

A related potential application of biobehavioral research in cancer focuses on adoptive immunotherapy, which involves the cultivation of the patient’s leukocytes with IL-2 to expand a population of lymphokine-activated killer (LAK) cells known to have antitumor activity. This treatment has been employed in melanoma and renal cell carcinoma, as well as after HSCT to boost activity against MRD. Although speculative, the central role of the cellular immune response in the success of both HSCT and adoptive immunotherapy provides an opportunity for biobehavioral factors to influence treatment outcomes.

In conclusion, accumulating evidence suggests the importance of considering behavioral risk factors in the care of cancer patients. Although delineation of mechanisms is still ongoing, there is compelling evidence that behavioral and psychosocial factors that activate the neuroendocrine stress response can alter immune, angiogenic, and inflammatory pathways important in the development, progression, and control of malignancy. Alongside conventional therapies, behavioral interventions incorporating cognitive-behavioral, mindfulness, supportive, and stress management approaches as well as novel pharmacologic strategies targeting stress response pathways have the potential to improve the care, well-being, and survival of individuals with cancer.

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Figure 1.

In addition to known biomedical risk factors, this biobehavioral model of cancer control illustrates the contributions of behavioral risk and resilience factors to cancer outcomes. Stress-related behavioral factors can activate (or inhibit) the hypothalamic pituitary adrenocortical (HPA) axis and sympathetic nervous systems (SNS). The products of these pathways, including glucocorticoids, catecholamines, and other neuroendocrine factors, have downstream effects on physiological mechanisms in the tumor microenvironment important for the control of malignancy. These include the modulation of cellular immune processes relevant to tumor surveillance and containment, inflammation, and other pathophysiological processes critical to cancer growth and progression, including angiogenesis, invasion, and tumor-promoting cell-signaling pathways. Alteration of these physiological processes can encourage or inhibit tumor progression and metastasis. The potential effects of tumor- and treatment-derived inflammatory processes on depression (dashed arrow) and quality of life are also illustrated.