

Biobehavioral Pathways to Cancer Incidence, Progression, and Quality of Life

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Abstract

Cancer research within the fields of psychoneuroendocrinology and psychoneuroimmunology has made substantial progress in understanding how psychological factors impact cancer. Although the pathways by which stress “gets under the skin” to impact cancer incidence, progression, and quality of life are not yet fully understood, the answers to key questions about how stressful life events and the negative emotions they generate can impact cancer initiation, progression, and survivorship have advanced quite dramatically. In this review, we summarize the state of the science in a way that is accessible to a broad audience. We then discuss future directions in cancer research, with a focus on ways psychological science can contribute to the next generation of cancer care.

Keywords

psychoneuroimmunology, cancer, inflammation, HPA axis, autonomic nervous system

Psychological factors have long been suspected to influence health processes related to cancer. Cancer research within the field of psychoneuroendocrinology and psychoneuroimmunology has made substantial progress in understanding these mechanisms. Advances in our fundamental knowledge of cancer biology (Hanahan & Weinberg, 2011), cancer immunology (Rosenberg, Yang, & Restifo, 2004), and neural regulation of cancer (Cole, Nagaraja, Lutgendorf, Green, & Sood, 2015) are enabling psychologists and biological scientists to answer questions surrounding how psychological factors impact those diagnosed and treated for cancer. In this review, we seek to provide an accessible overview of the current state of the science that is digestible to a broad audience.

Cancer is a category of diseases that involve abnormal cell growth. Cancer is life threatening when it metastasizes (i.e., spreads to other parts of the body). This occurs when cancer cells are able to circulate through the blood stream via penetration of lymphatic and blood vessels to spread to other organs (Michor, Iwasa, & Nowak, 2004). There is some evidence to suggest that stress is associated with cancer incidence; however, the evidence is equivocal and primarily based on

large epidemiological studies without examination of biological mechanisms. For example, Lillberg et al. (2003) found that women who experienced stressful life events (e.g., divorce, death of a husband, death of a relative or close friend) during a 5-year baseline period were more likely to be diagnosed with breast cancer during the next 15 years than those who did not experience these events. It is important that, in their analyses, the authors accounted for age, marital status, social class, age at first full-term pregnancy, number of children, body mass index, smoking status, and physical activity.

Psychological stress also promotes abnormal cells by impairing DNA repair. DNA is the inherited material in every cell of a person’s body. An important property of DNA is that it can replicate, or make copies of itself. Under optimal conditions, a cell can identify and correct damage to DNA molecules that encode its genome (i.e., DNA repair). Carcinogens are elements that can cause cancer by damaging cellular DNA, resulting in

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the production of abnormal cells (Flint, Baum, Chambers, & Jenkins, 2007). The body defends against this damage by producing enzymes that destroy chemical carcinogens and repair cellular DNA by eliminating abnormal cells (Cohen, Marshall, Cheng, Agarwal, & Wei, 2000). However, stress can dysregulate this process. Using a noncancerous population of medical students, researchers performed a host-cell reactivation assay to determine whether individuals who were in a highly stressful situation (i.e., studying for an academic medical exam) demonstrated a poorer ability to repair damaged DNA (Cohen et al., 2000). Results confirmed that the cells of those who reported more stress demonstrated a poorer ability to self-repair damaged DNA. In addition, glucocorticoids have been shown to impair expression of DNA repair genes (Herr et al., 2003). Studies such as these provide evidence that psychological stress may impact cancer initiation and progression. Despite this, the questionable prognostic value in examining the impact of peripheral markers on damaged DNA and cellular markers of immunity to cancer progression has moved the field toward focusing on the tumor itself.

In a study of older men and women, those who were depressed over three separate time points were more likely to develop cancer than those who were not (Penninx et al., 1998). In this study, the authors adjusted for several confounders, such as age, sex, ethnic origin, cigarette smoking alcohol intake, physical disability, and body mass index. However, other well-conducted studies have shown no such link (e.g., Johansen & Olsen, 1997). 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 survivorship (Lutgendorf, Sood, & Antoni, 2010). Accordingly, the rest of this article focuses on how psychological factors impact cancer progression (rather than tumor initiation), as well as the survivorship period.

The Fight-or-Flight Response

Before explaining how psychological factors impact cancer, we briefly summarize hormones that are implicated in the stress response (see Fig. 1). Psychological stress promotes the fight-or-flight response resulting in autonomic nervous system (ANS) and hypothalamic-pituitary-adrenal (HPA) axis activation. Catecholamines are released as a reaction to the sympathetic nervous system during the fight-or-flight response, which promotes increased heart rate, blood pressure, and blood glucose levels. Catecholamines that are released in the bloodstream include epinephrine and norepinephrine. The HPA axis, a major part of the neuroendocrine

system, controls reactions to stress and regulates many bodily functions, including the immune system by way of glucocorticoids (cortisol in humans), which are released from adrenal cortex (Melmed, Polonsky, Larsen, & Kronenberg, 2015).

Psychological Stress and Immunosuppression

The production of glucocorticoids can suppress the cellular immune system, an aspect of the immune system responsible for eliminating precancerous cells (Grivennikov, Greten, & Karen, 2010). Indeed, chronic stress, depression, and perceptions of low social support are associated with impaired cellular immunity (Andersen et al., 1998). As shown in Figure 1, cell-mediated reactions are predominately a T-cell (a lymphocyte processed by the thymus gland) response to any cell that displays aberrant major histocompatibility complex markers (a set of cell surface proteins that promote recognition of foreign molecules), including tumors (Reiche, Nunes, & Morimoto, 2004). Abnormal cellular immune responses are found in patients with many different types of cancer (Reiche et al., 2004).

Animal studies provide experimental evidence for relationships between stress and tumor progression, allowing for stronger causal inferences than human studies allow. In a recent study, a breast cancer tumor was induced in two groups of female rats. In one group, rats were isolated to enhance glucocorticoid levels. In another group, rats were allowed to remain together in a large cage. The isolated group developed more tumors than the control group, and the volume of tumors was greater because of the production of glucocorticoids (De la Roca-Chiapas et al., 2016).

Psychological Stress, Tumorigenesis, Tumor Survival, and Metastasis

Several findings have suggested that catecholamines and adrenergic receptors (a class of protein-coupled receptors that are targets for catecholamines) promote progression (Eng et al., 2014; Powe et al., 2011; Tabassum & Polyak, 2015). Indeed, tumors that are graded as high (i.e., more likely to grow and spread) show increased expression of adrenergic receptors, indicating that adrenergic receptors play an important role in promoting tumor progression (Zhang et al., 2011). In addition to a role in cell survival, adrenergic receptor signaling can promote metastasis (see Fig. 1), which is the development of secondary malignant growths at a distance from a primary site of cancer (Sloan et al., 2010). Adrenergic receptor expression has been found in mammary tumors (breast cancer),

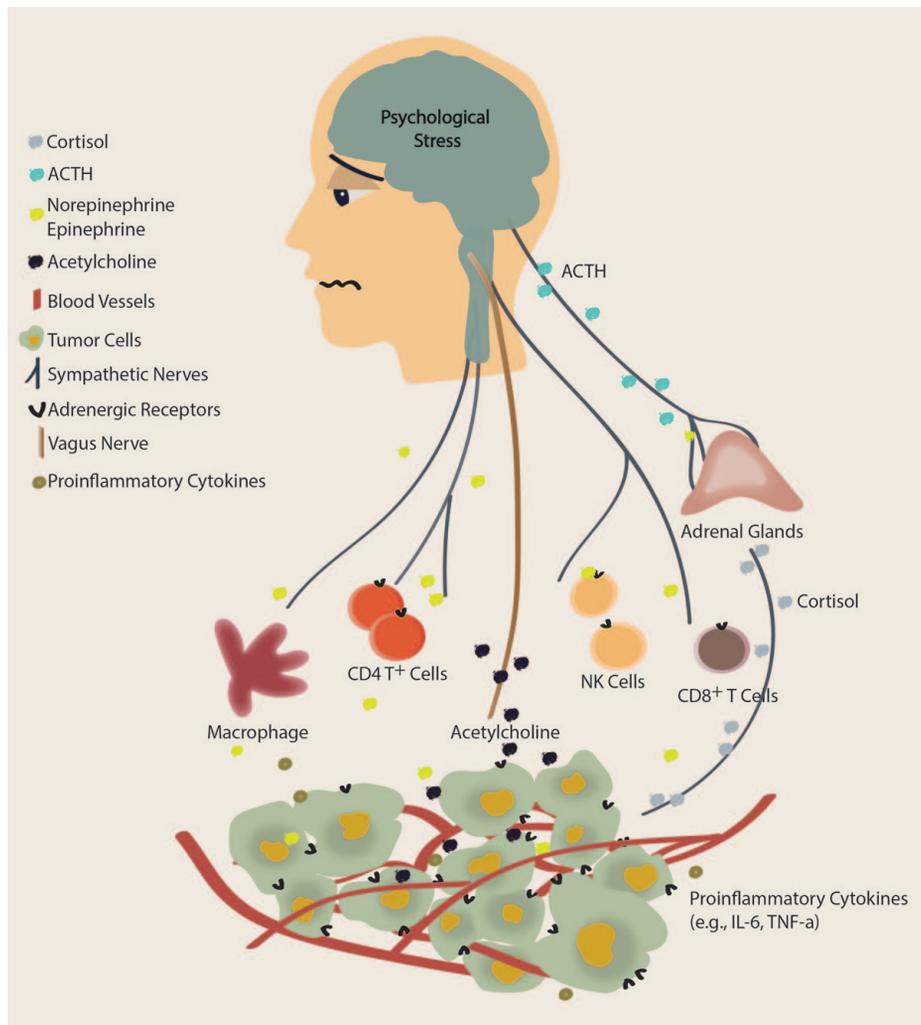


Fig. 1. Various mechanisms underlying the association between stress and cancer. Key pathways include the adrenocorticotropic hormone (ACTH) stimulating the adrenal gland, which produces cortisol. Cortisol downregulates immune function (dampening T cells, NK cells, and macrophages) and may directly impact the tumor environment. Vagal activity promotes acetylcholine release, which is anti-inflammatory. Sympathetic activity impacts adrenergic receptors, which directly affect the tumor environment. Proinflammatory cytokines play critical roles at different stages of tumor development, including initiation, promotion, malignant conversion, invasion, and metastasis. IL = interleukin; TNF = tumor necrosis factor.

melanoma (a type of skin cancer), and pancreatic, lung, and prostate cancer cells (Cole et al., 2015; Lutgendorf & Sood, 2011).

Up to this point, we have focused on the notion that stress and depression are the key culprits impacting dysregulated autonomic, neuroendocrine, and immune dysregulation; however, people's life history and current social relationships also appear to play an important role. Evidence is mounting for a cumulative-life-stress model of autonomic, neuroendocrine, and immune dysregulation that dates to childhood experiences (Fagundes, Glaser, & Kiecolt-Glaser, 2013). In a study examining the impact of stress on basal cell carcinoma (BCC; a highly immunogenic tumor—meaning the

immune system recognizes the tumor as foreign and thus attempts to attack it), both maternal and paternal emotional maltreatment interacted with the occurrence of severe life events to predict the local immune response to the tumor. Among patients who had experienced a severe life event within the past year, those who were emotionally maltreated by their mothers or fathers as children had a poorer immune response to the tumor. Emotional maltreatment was unrelated to BCC immune responses among those who did not experience a severe life event (Fagundes, Glaser, et al., 2012a).

Ovarian tumors are also highly immunogenic. In accord with the vast literature demonstrating the impact

of social support on health, Lutgendorf and colleagues (2008) examined how social support impacts the tumor environment. Ovarian cancer patients who reported elevated depressive symptoms, chronic stress, and low social support showed elevations of tumor-associated macrophages, which have been linked to increased metastasis, angiogenesis, and tumor aggressiveness. Accordingly, in addition to stress and depression, other key psychological factors, such as social support and early life stress, are impactful.

The death of cells that occur as a normal and controlled part of development is essential to prevent cancer. This process is called apoptosis. Apoptosis is a process by which cell death occurs in multicellular organisms. The mechanism of apoptosis is complex and involves many pathways (Fernald & Kurokawa, 2013). In particular, adrenergic receptors impair apoptosis (Fernald & Kurokawa, 2013). In a pancreatic cancer cell line, when adrenergic receptors were inhibited, the pathways regulating tumor survival decreased, and the patient responded better to cancer treatment (Zhang et al., 2011). Prostate cancer is also augmented by adrenergic receptors (Sastry et al., 2007). Catecholamines have been implicated through similar mechanisms in a variety of cancer cells by promoting an antitumor immune response and impacting tumorigenesis, growth, and metastasis in some cancers (i.e., melanoma, breast, ovarian, and leukemia; Eng et al., 2014).

Psychological factors also play an important role in metastatic growth. Successful metastatic spread requires several sequential steps, including angiogenesis (i.e., formation of new blood vessels), proliferation (i.e., an increase in the number of cells as a result of cell growth and division), invasion (i.e., the ability to penetrate surrounding tissues), embolization (i.e., blockage of blood vessels), and colonization of a new secondary site. In a provocative study that investigated the role of neuroendocrine activation in cancer progression using a mouse model of breast cancer (Sloan et al., 2010), stress-induced neuroendocrine activation induced a 30-fold increase in metastasis to distant tissues, including the lymph nodes and lung. These were explained by adrenergic signaling, which increased the number of macrophages (a type of white blood cell) in the primary tumor. It is interesting that treatment of stressed animals with a pharmacological agent that blocks sympathetic activity at the level of the receptor (propranolol) reversed the stress-induced macrophage infiltration (Sloan et al., 2010).

As shown in Figure 1, inflammation also promotes metastasis (Tabassum & Polyak, 2015). It is now well established that chronic stress can effectively prime the inflammatory response (Todoric, Antonucci, & Karin, 2016). As previously mentioned, cortisol is also released

under conditions of stress and depression. Although cortisol acutely inhibits inflammation (Barnes, 1998; Brattsand & Linden, 1996), chronically high cortisol levels can *sometimes* lead to glucocorticoid insensitivity. Glucocorticoid insensitivity allows immune cells to produce proinflammatory cytokines in an unregulated environment, thereby raising inflammation (Fagundes, Glaser, & Kiecolt-Glaser, 2013). Within tumor cells, activation of adrenergic receptors drives inflammation and, in turn, promotes angiogenesis. Inflammation promotes cancer invasion when a growing tumor moves beyond mutant cells and adjacent tissues and then travels to other sites. These are key mechanism underlying metastasis and eventual death (Tabassum & Polyak, 2015). Accordingly, stress-induced inflammation is a pathway by which psychological stress promotes tumor survival and metastasis.

Cancer Survivorship and Psychoneuroimmunology

Some of the most promising and clinically relevant work in the field of psychoneuroimmunology and cancer has focused on how the immune system interacts with the brain to contribute to cancer survivors' post-treatment symptoms, such as fatigue. Persistent low-grade inflammation leads to continued fatigue. Bower (2007) has demonstrated that cancer survivors who report persistent fatigue are characterized by higher levels of inflammation after treatment than nonfatigued cancer survivors. Furthermore, fatigued cancer survivors have cells that have greater proinflammatory tendencies, manifest in exaggerated cytokine responses to a challenge (Collado-Hidalgo, Bower, Ganz, Cole, & Irwin, 2006). Although the source of inflammation in cancer-related fatigue is likely multifaceted, psychological stress and depression likely play an important role given that stress can prime the inflammatory response (Fagundes, Glaser, Hwang, Malarkey, & Kiecolt-Glaser, 2013). Indeed, dysregulated cortisol production, lower parasympathetic activity, and higher sympathetic activity have also been shown to impact cancer-related fatigue (see Bower & Lamkin, 2012, for a review). Other work has demonstrated that early life stress, poor social support, and cumulative stress are associated with cancer-related fatigue (Bower, Crosswell, & Slavich, 2014; Fagundes, Lindgren, Shapiro, & Kiecolt-Glaser, 2012).

Future Work in Psychoneuroimmunology and Cancer

Hanahan and Weinberg (2011) identified the ability of tumors to evade the immune system as an emerging "hallmark of cancer" and highlighted stress-induced

pathways as an enabling characteristic of cancer development. These fundamental principles, grounded by an improved understanding of the immune system as a brake and an accelerator of cancer development and progression (Hanahan & Weinberg, 2011), have paved the way for “breakthrough” cancer treatment approaches, such as immunotherapy (Couzin-Frankel, 2013). Quite generally, cancer immunotherapies utilize the immune system to eliminate cancer cells by promoting recognition of specific molecules on the cancer-cell surface. On the basis of evidence that adrenergic receptor signaling impacts tumor progression and survival and modulates the activity of immune cells, it is reasonable to surmise that direct and indirect effects of the sympathetic nervous system are capable of modulating the efficacy of immunotherapies and other targeted therapies, such as hormone therapies, signal transduction inhibitors, gene expression modulators, apoptosis inhibitors, and angiogenesis inhibitors (Cole et al., 2015). The efficacy of these new therapies is contingent on the ability to precisely identify for whom and under what conditions a targeted approach is likely to produce the desired outcome.

Conclusion

The answers to key questions about how stressful life events and the negative emotions they generate can impact cancer initiation, progression, and survivorship have advanced quite dramatically. The field has moved from investigating epidemiological associations to exploring biological mechanisms with a focus on the tumor environment. The promise of immunotherapy to eliminate cancer cells by promoting recognition of specific molecules on the cancer-cell surface provides an exciting opportunity for the fields of psychoneuroendocrinology and psychoneuroimmunology to play an important role in the next generation of cancer care.

Recommended Reading

- Bower, J. E., & Lamkin, D. N. (2012). (See References). A well-written summary of research reviewing the biobehavioral mechanisms that underlie cancer-related symptoms.
- Eng, J. W. L., Kokolus, K. M., Reed, C. B., Hylander, B. L., Ma, W. W., & Repasky, E. A. (2014). (See References). A review of work showing that the sympathetic nervous system impacts cancer cells, immunosuppression, and immunotherapeutic response.
- Lutgendorf, S. K., & Sood, A. K. (2011). (See References). A summary of the biobehavioral factors underlying cancer progression.

Declaration of Conflicting Interests

The authors declared that they had no conflicts of interest with respect to their authorship or the publication of this article.

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