Stress, depression, the immune system, and cancer

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The links between the psychological and physiological features of cancer risk and progression have been studied through psychoneuroimmunology. The persistent activation of the hypothalamic-pituitary-adrenal (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. Here, we overview the evidence that various cellular and molecular immunological factors are compromised in chronic stress and depression and discuss the clinical implications of these factors in the initiation and progression of cancer. The consecutive stages of the multistep immune reactions are either inhibited or enhanced as a result of previous or parallel stress experiences, depending on the type and intensity of the stressor and on the animal species, strain, sex, or age. In general, both stressors and depression are associated with the decreased cytotoxic T-cell and natural-killer-cell activities that affect processes such as immune surveillance of tumours, and with the events that modulate development and accumulation of somatic mutations and genomic instability. A better understanding of the bidirectional communication between the neuroendocrine and immune systems could contribute to new clinical and treatment strategies.

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Figure 1. Psychological state can affect the outcome of disease.

The idea that psychological states can affect the outcome of human disease is an old one. Around AD 200, Galen[1] wrote that melancholic women were more susceptible to "swellings" of the breasts than were sanguine women. In 1936, Hans Selye defined stress physiologically as the state in which the sympathoadrenomedullary system and the limbic-hypothalamic-pituitary-adrenal axis (HPA) are co-activated.[2]

Our understanding of the interactions between the HPA axis and inflammatory reactions mediated by the immune system has expanded greatly, with many studies showing that psychological stress (figure 1) can down-regulate various parts of the cellular immune response. Communication between the CNS and the immune system occurs through chemical messengers secreted by nerve cells, endocrine organs, or immune cells, and psychological stressors can disrupt these networks.

Evidence for an interaction between the CNS and the endocrine and immune systems derived from observations that neurotransmitters such as norepinephrine, serotonin, dopamine, and acetylcholine; neuropeptides such as enkephalins, substance P, vasoactive intestinal peptide, corticotrophin-releasing factor, and neuropeptide Y; neurohormones such as growth hormone, adrenocorticotropin hormone, and prolactin; and adrenal hormones such as corticosteroids and epinephrine affect immune function both in vivo and in vitro, and receptors for these molecules are present on lymphocytes and macrophages. The neuroendocrine and immune systems share common signal mediators and receptors, suggesting that the brain has an immunoregulatory role and the immune system a sensory

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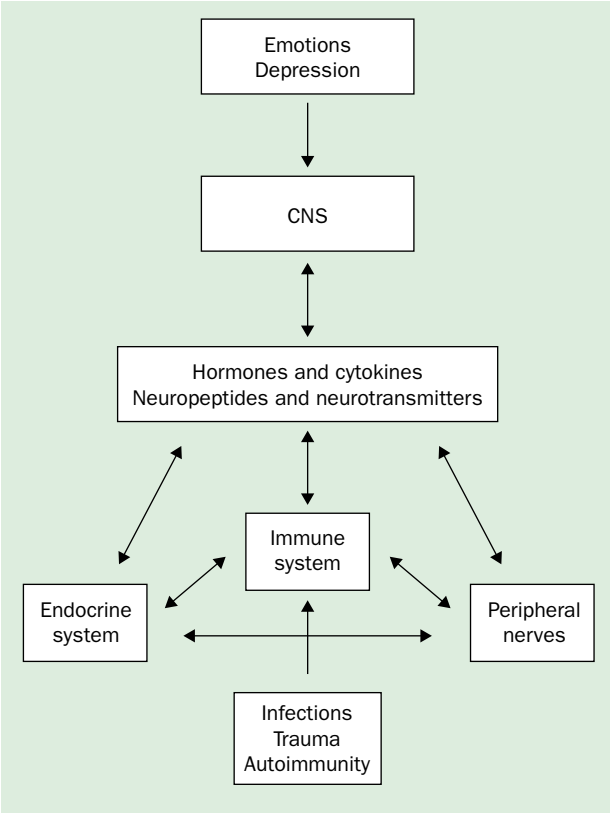

Figure 2. Network of bidirectional communication between CNS, peripheral nervous systems, endocrine, and immune systems.

function.[3–5] The cytokines interleukin 1, tumour necrosis factor (TNF) α, interferon α, and interferon γ secreted from activated immune cells can in turn change the function of the HPA axis.

The interaction with the immune system involves most of the brain, where high to moderate densities of receptors for interleukin 1 have been detected in different structures of the mouse CNS. Many of these mediators are produced locally by glial or neuronal cells and have functions similar to those of neurotransmitters. Interactions between emotions and immune functions might underlie the increased clinical susceptibility to infectious diseases or malignant tumours. In turn, diseases that greatly activate the immune system, such as trauma, sepsis, and autoimmune disorders, can entail psychopathological manifestations (figure 2).[5]

Physiological response to stress

Stressful experiences include physical stressors such as pathogens and toxins, and psychological stressors such as major life events, trauma, abuse, or factors related to the environment in the home, workplace, family, or neighbourhood. The ability to adjust or habituate to repeated stress is also determined by the way a person perceives a situation.[6]

The major neural pathways activated by stressors are the HPA axis and the sympathetic nervous system.[1–3,5,7–9] Neurosensory signals are ultimately processed in the paraventricular nucleus of the hypothalamus and in the locus coeruleus-noradrenergic centre. In response, the hypothalamus secretes corticotropin-releasing factor (CRF) and arginine vasopressin, which activate the HPA axis, leading to release of pituitary peptides produced by differential cleavage of pro-opiomelanocortin, most notably adrenocorticotrophic hormone, enkephalins, and endorphins. Adrenocorticotrophic hormone induces downstream release of glucocorticoids from the adrenal cortex. The activation of the sympathetic nervous system by CRF is mediated by direct innervation of the locus coeruleus in the brainstem, which leads to widespread release of norepinephrine throughout the brain and peripheral tissues. Activation of the sympathetic nervous system also stimulates the release of CRF by hypothalamic paraventricular nuclei. Thus, the stress-response system seems to function as a positive, bidirectional feedback loop: activation of one component of the system stimulates the other components (figure 3).[8–10]

Stress experiments suggest that the plasma concentration of epinephrine is inversely related to specific immune functions of lymphocytes and monocytes. Catecholamines and opiates are reported to be immunosuppressive. Furthermore, many studies have suggested that corticosteroids, which are found in high concentrations during stress, have important immunosuppressive effects on the functions of lymphocytes and macrophages, and might affect their circulation patterns. Corticosteroids also decrease the production of many cytokines and mediators of inflammation, and decrease the effects of some inflammatory molecules on various target tissues. Although acute stress sometimes increases secretion of growth hormone and prolactin, chronic stress is associated with inhibition of growth-hormone secretion secondary to CRF-stimulated somatostatin and with the inhibition of prolactin mRNA expression.[7–11]

Cytokines are soluble mediators released by various cells both at the periphery by macrophages and lymphocytes, and in the brain by astrocytes and microglia, which operate within a complex network and act either synergistically or antagonistically. Production of cytokines has been divided into two broad categories depending on the functional profile of the secreting T-helper cells: type 1 helper cells (Th1) generally mediate the cellular immune response through the activities of cytotoxic lymphocytes, natural-killer (NK) cells and macrophages and include production of the cytokines interferon γ, TNF α, and interleukin 2; type 2 helper cells (Th2) enhance immune reactions mediated by antibodies, and include production of interleukin 4, interleukin 5, interleukin 6, and interleukin 10. Th1 and Th2 cells can be cross-inhibitory; interleukin 4 and interleukin 10 released by Th2 cells exert anti-inflammatory effects, which suppress the activity of Th1 cells and stimulate Th2 cells and humoral immune responses.[12] The process by which Th2 cells suppress production of interferon γ that is derived from Th1 cells is more complicated: presence of interleukin 10 suppresses the synthesis of interleukin 12 by monocytes, macrophages, and B cells. Shifts in the balance of type-1 and

type-2 reactions mediated by stress have been reported.[8,9,13–16] Among the cytokines produced in the early innate immune response, interleukin 12 is a key inducer of cell-mediated immunity, and stimulates differentiation of CD4-helper T lymphocytes into T-helper cells that produce interferon γ. Glucocorticoids, norepinephrine, epinephrine, and histamine inhibit the production of human interleukin 12 by antigen-presenting cells such as monocytes, macrophages, and dendritic cells, whereas they do not affect the production of interleukin 10. Because interleukin 12 and TNF α promote Th1 responses and cellular immunity, whereas interleukin 10 suppresses both the production of interleukin 12 and the Th1 activity and stimulates Th2 and humoral immune responses, the neuroendocrine mediators released by stress might cause a selective suppression of Th1 responses. In addition to the inhibitory effects of the neuroendocrine mediators on Th1 cells, the production of interleukin 10 also inhibits the activity of these cells. The mechanism of inhibition of Th1 but not Th2 cells explains the shift from the Th1 to Th2 immune response, which impairs the cellular immune responses against various infections and some tumours that are normally mediated by Th1 response (figure 4). Conditions that contribute to a substantial increase or decrease of local or systemic concentrations of these mediators via modulation of interleukin 12 and the balance between TNF α and interleukin 10 might also play a part in the induction, expression, and progression of some autoimmune and cardiovascular diseases, osteoporosis, rheumatoid arthritis, type 2 diabetes, allergic or atopic reactions, and the growth of some tumours. These conditions include acute or chronic stress, severe and exhaustive exercises, serious surgical procedures or traumatic injuries, major burns, severe ischaemia or hypoxia, pregnancy, and the postpartum period.[9,13–16]

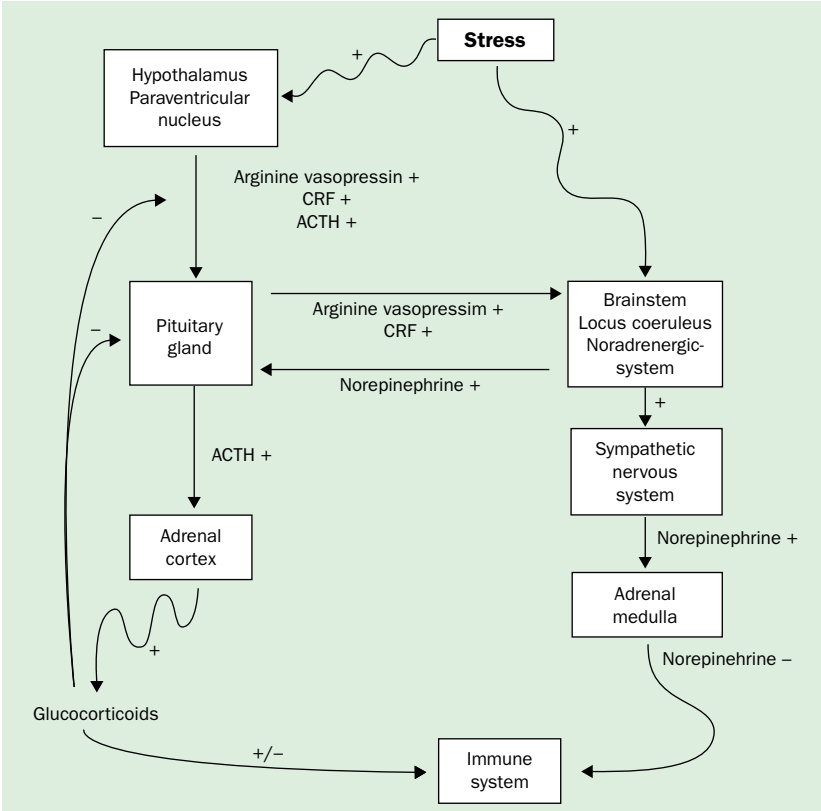

Figure 3. Interactions between nervous, endocrine, and immune systems. Pituitary cells and sympathetic nervous system are positively regulated by hypothalamic factors, including corticotropin-releasing factor (CRF) and arginine vasopressin. Adrenocorticotropic hormone (ACTH) released by the pituitary gland evokes glucocorticoid synthesis by adrenal cortex. CRF and ACTH production is inhibited by glucocorticoid feedback. Norepinephrine is also released from sympathetic nervous system. +, stimulation; –, inhibition; +/–, stimulation and inhibition.

Role of stress and depression

The effect of psychological factors on cancer depends very much on the type of tumour involved. Moreover, the validity of many of the data has been questioned because retrospective studies tend to show associations that are linked in the memory of individuals, and much information about real-life stressors could possibly be lost, whereas unliked phenomena are remembered less well. These observations, which are the core of psychosomatic medicine, have been rejected or ignored by many scientists until recently because of the lack of plausible mechanisms linking the nervous system to immune function. However, studies in animals have suggested that stress renders them more susceptible to diseases and impairs the function of the immune system.[17,18]

Animal studies

A wide variety of stressors have been used in studies of environmental effects on immunological function.[17] A classic example is that spleen cells isolated from mice exposed to daily sound stress had a reduced ability to respond to test mitogens. [19] Other studies[1] have shown that innate lymphocytes also have a reduced ability to kill foreign target cells, known as NK activity. Rats unable to escape from electric shock had earlier tumour appearance, enlarged tumours, and decreased survival time compared with those given the opportunity to escape the shock. Inescapable, but not escapable, shock also significantly impairs tumour rejection[20] and the lymphoproliferative response to lectins.[21] Studies[8,22,23] of the effects of stressful conditions on several cell immune responses have also been reviewed. Stressful conditions can greatly suppress the immune response of blood and spleen lymphocytes, including T-cell mitogenesis, production of IgG2a (controlled by Th1 cells) but not IgG1 (controlled by Th2 cells), NK cell activity, and production of interleukin 2 and interferon γ.[8] Expression of interleukin 2

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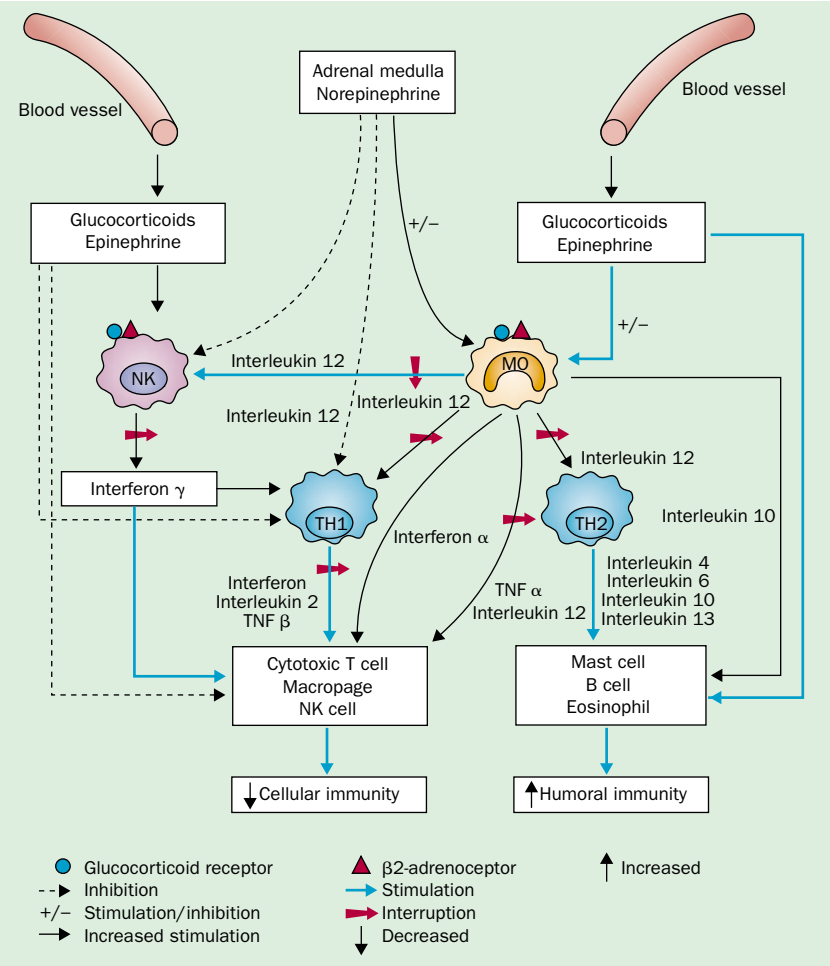

Figure 4. Systemic effects of the stress hormones glucocorticoids and catecholamines, both secreted by the adrenal gland, and norepinephrine released by sympathetic nerve terminals, on the immune system. These soluble mediators inhibit some non-specific and specific parts of the cellular immune response and stimulate some specific parts of the humoral immune response. Solid lines are stimulation and dashed lines are inhibition. NK, natural-killer cells; MO, macrophage; Th1, T-helper lymphocyte type 1 cells; Th2, T-helper lymphocyte type 2 cells; TNF, tumour necrosis factor.

receptors was also reduced in lymphocytes from animals exposed to stressful conditions, thereby indicating that a reduced ability of lymphocytes to respond to interleukin 2 contributes to the reduction in the immune response. By contrast, other studies with different stressors and animal strains have shown different results, such as the finding that chronic stress significantly diminished both the Th1 (interleukin 2 and interferon γ) and Th2 (interleukin 10) cytokine responses[8] but did not change NK cell activity or the concentrations of cytotoxic T lymphocytes, suggesting that the increase in tumour metastases is not associated with an observed change in specific or non-specific cytotoxic responses.[23] These contradictory results highlight the complexity of interactions between behaviour, the brain, immune system, and the stressor. Genetic background of the animal, its previous history, nature of the stressor, and type of immune response generated are some of the interacting factors that determine the magnitude and direction of stress-induced changes in disease outcome.[23]

Stress has also been associated with low concentrations of O6-methyl-transferase, an important DNA repair enzyme induced in response to carcinogen damage, in the spleen lymphocytes of rats subjected to rotational stress,[24] and an increased frequency of exchanges between sister chromatids in rat cells.[25] Such exchanges reflect the cytogenetic damage and genomic instability that could be preclinical markers for cancer.[26] Other examples include the observations of immune response and neoplastic disease.

Two stress paradigms (forced swimming and abdominal surgery) were used to assess the extent to which stress-induced alterations in NK cell activity underlie increased susceptibility to tumour development in F344 rats. Swimming stress increased the mortality and metastatic development of two tumours sensitive to NK activity but not the metastases of an NK-insensitive tumour. In both stress paradigms, stress suppressed NK activity for a duration that paralleled its metastasis-enhancing effects on the NK-sensitive tumour. Data indicate that stress-induced suppression of NK activity is sufficient to cause enhanced tumour development. Under some stressful conditions, suppression of NK activity is the primary mediator of the tumour-enhancing effects of stress, whereas under other conditions, additional factors play an important part.[27]

Some studies have analysed the effects of maternal stress on immune competence. One study found a marginal decrease in NK-cell activity in juvenile (30-day-old) prenatally stressed male rats and a small increase in NK cell cytotoxicity in the adult prenatally stressed offspring of both sexes.[28] Also, decreased macrophage spreading and phagocytosis, and increased growth of both the ascitic and solid forms of Ehrlich tumour have been reported.[29]

The lack of social interactions among animals is comparable to the situation of humans who feel isolated and would be helpful for investigation of the modulatory role of psychological stress in tumour development. Evidence with rodents has showed that social stressors decrease NK cell activity and enhance the metastasis of transplantable tumours.[30] The effect of social stress on the vulnerability of male BALB/c mice to developing liver metastasis of colon 26-L5 carcinoma cells was investigated in terms of time span and incidence of metastasis formation, the extent of metastatic tumour burden, chemotherapy response, and

survival time.[31] The data showed that resistance to the development of metastasis was significantly impaired, with accelerated manifestation of tumour colonies, increased incidence of metastases, and enhanced mortality, as well as a reduced response to chemotherapy. Isolation stress could affect various steps during tumour metastasis, including the direct stimulation of tumour growth at metastatic sites and the stimulation of angiogenesis through HPA activity and through the suppression of cell immunity, facilitating tumour metastasis. Decreased spreading of macrophages and phagocytosis, increased release of hydrogen peroxide by macrophages, increased growth of the ascitic form of Ehrlich tumour, and a higher increment of serum corticosterone concentrations were also seen in stressed mice.[32] On the basis of these data, stress conditions might promote the initiation and progression of cancer by impairment of the immune functions that are relevant to immune surveillance, mainly NK cell activity, one of the immune mechanisms against the development of some types of tumours.

Human studies

The effects of biological stressors on various parts of immunological function and the association with cancer have been investigated in transverse and longitudinal prospective studies.[33,34] At the cellular level, stressed and depressed patients had an overall leucocytosis, 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.[35–38] At the molecular level, serum and plasma concentrations of basal cortisol, complement components C3 and C4, specific antibodies against herpes simplex virus type 1 and Epstein Barr virus, and acute-phase proteins were higher in depressed patients than in healthy controls.[35–39] Although most of the published studies showed impairment of various immune factors, sample characteristics, the types of immunity-challenging, psychological stressors, and their methods should be investigated carefully. The homogeneity of the populations involved causes some limitations in the generalisation of findings obtained from the study samples to the population as a whole. Findings on young and healthy people should only cautiously be extrapolated to elderly or middle-aged individuals. The well-known differences in immune status between young and older people should suggest caution in assessing results from research that includes groups with large age ranges. The stressor exposures assessed in the reviewed studies differed according to the acute and chronic dimension and to their intensity, and the timing and duration of stress might substantially affect the nature of the effects of stress on immune function. During acute stress, stress hormones can help enhance immune function by informing the immune system about impending challenges that may be imposed by a stressor. However, chronicity has been shown to have an adverse effect on health, leading the organism to exhaustion, distress, and disease.

Another part of the immune response affected by psychological stress is cytokine secretion. An increase in plasma concentration and in-vitro production of interleukin 1, interleukin 6, soluble interleukin 2, and interleukin 6 receptors was reported in patients with major depression, suggesting that concentrations of proinflammatory cytokines in patients with major depression correlate with disease severity and HPA activity.[40–42] However, measurement of plasma concentrations of cytokines is not very reliable and values are often undetectable or highly variable and therefore difficult to interpret. In vitro cytokine secretion provides more useful information about the quantity and activity of specific cytokines.[42]

Conjugal bereavement has been the subject of several studies done to investigate a possible association with increased morbidity and mortality. The first study[43] showed that T-lymphocyte responses to low doses of phytohaemagglutinin were reduced after the death of the spouse, during which time active bereavement occurred. Lymphocyte stimulation with mitogens was assessed in 15 spouses of women with advanced breast carcinoma and the lymphoproliferative responses were significantly suppressed in the first 2 months after the death of a spouse compared with pre-bereavement levels.[44] However, in these two related studies the bereaved people did not systematically receive a standardised psychiatric diagnosis or mood rating, with a consequent difficulty in the determination of whether the reported immunocompromise was caused by the stress of normal bereavement or by some other occult psychiatric disorder, such as major depression.[33] In another study,[45] bereaved spouses showed reduced NK activity and increased plasma cortisol concentrations compared with controls. Anticipatory bereaved women also showed significant reductions in NK activity.

Health risks associated with separation and divorce are thought to be greater than those associated with bereavement.[46] Separated or divorced women had a poor immune function in terms of qualitative (or functional) and quantitative features of immunity. Women who had separated from their husbands within the previous year had poorer immune function than did sociodemographically matched married women, with significantly poorer proliferation in response to mitogens, significantly lower proportions of NK cells and helper T cells, and significantly higher antibody titres to Epstein-Barr virus capsid antigen.[47] The lower numbers of NK cells in the separated or divorced group and the persistent depression might have had consequences at the molecular level in terms of the speed and quality of DNA repair that could mediate an increased cancer risk.[48] In a study[49] of newlywed couples, those who were more negative or hostile during a discussion of marital problems with the spouse showed a greater reduction in NK-cell activity 24 h later. Although the sample size of most of the reviewed studies about the effect of conjugal bereavement, separation, and divorce was quite small, the data obtained emphasise the effect of severe life events on the immunological status and consequent health of healthy individuals.

Another extensively investigated topic is the effect of chronic stress on sympathetic nervous system activity and

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NK-cell cytotoxicity in individuals who cared for patients with Alzheimer's disease. Plasma concentrations of neuropeptide Y were significantly raised in older caregivers, and negatively correlated with NK-cell activity among caregivers; however, caregivers and controls did not differ in terms of NK-cell activity.[50]

A study[51] showed that stressful negative life events and pessimism were associated with lower NK-cell cytotoxicity and T-cytotoxic and suppressor-cell (CD8, CD3) percentage in black women co-infected with HIV-1 and human papillomavirus (HPV). A pessimistic attitude might be associated with immune decrements, and possibly poor control over HPV infection and an increased risk for future progression from cervical dysplasia to invasive cervical cancer in minority women co-infected with HIV-1 and HPV.

Examination stress in university students has been the subject of several studies. In a follow-up study,[52] examination stress was found to reduce NK-cell activity, which correlated with the degree of loneliness. Academic stress has also been associated with significant changes in antibody concentrations to latent herpes virus, suggesting changes in cell immunity.[53]

One of the more consistent observations reported in studies of depression and immunity in adults and children is lower NK-cell activity.[54] Young adults with major depression had more circulating leucocytes and granulocytes, fewer CD56-positive (NK cells), and when the number of circulating NK cell was controlled, lower NK-cell activity was noted. The data suggested that major depression in young adults is associated with changes that involve mainly NK cells and some, but not all, of these immune changes differ from those found in older depressed adults. Psychological stress, assessed in 116 patients after a diagnosis of invasive breast cancer and subsequent surgery, inhibited the cellular responses relevant to cancer prognosis, such as NK-cell lysis and response of NK cells to recombinant interferon γ and the proliferative response of peripheral blood lymphocytes to plant lectins and to monoclonal antibody directed against the T-cell receptor.[55]

Despite the numerous reports documenting suppression of various indices of immune function in depression, contradictory studies have been reported in which researchers did not detect any significant alteration in some of the immune variables in patients who are depressed. These inconsistencies are suggested to be a result of, among other things, different experimental designs of the studies and the immunological assays, the assessment of various forms of depression of different severity or duration, the age of the patients, and other variables difficult to control that could affect the immune factors such as weight loss, malnutrition, sleep deprivation resulting from illness-related insomnia, tobacco use, alcohol and caffeine consumption, and activity and exercise levels.[33,41,56,57] Provocative and potentially important findings about the association between depression and carcinogenesis have been reported, showing that major depression interacted with cigarette smoking to promote lower NK-cell activity. Among 245 men, smokers who met diagnostic criteria for major depression had lower NK-cell activity than depressed non-smokers, suggesting that the immune changes could not be attributed to only the effects of smoking.[57]

Effects on cancer

Cancer is a heterogeneous group of diseases with multiple causes, and immunological involvement varies across different cancers. Cancers induced by chemical carcinogens might be less affected by psychological, behavioural, and immunological factors than are those associated with a DNA tumour virus, retrovirus insertion near a cellular oncogene, or other viruses such as Epstein Barr virus, which is immunogenic. Suppression of cellular immunity is associated with a higher incidence of some types of tumours, particularly Epstein Barr virus-associated lympho-proliferative diseases in organ-transplanted patients, and Kaposi's sarcoma and Epstein Barr virus-associated B-cell lymphoma in patients with AIDS.[58] A causal model in which the relation between stress, depression, and carcinoma is clarified was proposed.[59] Stress is associated with increased expression of interleukin 1, interleukin 6, and TNF α released from cells from the macrophage or monocyte lineage, with reduced expression of interleukin 2, interferon γ, and class-II MHC molecules, with down-regulated interleukin 2, and with reduced NK activity. Most organ-related carcinomas are associated with high concentrations of TNF α, which inhibits the activity of tyrosine phosphatase, which in turn results in diminished expression of the class-I MHC antigen on the cell surface, thus permitting malignant cells to escape immune surveillance. Therefore, stress and depression can foster tumour progression by inhibition of the expression of class-I and class-II MHC molecules and by reducing NK activity.

These notions could explain the increased occurrence of lymphatic and haematological malignant diseases, and of melanomas seen in a cohort of 6284 Jewish Israelis who lost an adult son. The incidence of cancer was increased in the parents of accident victims and in war-bereaved parents, compared with that in non-bereaved members of the population. Accident-bereaved parents also had an increased risk of respiratory cancer. Followed up for 20 years, the survival study showed that the risk of death was increased by bereavement if the cancer had been diagnosed before the loss, but not after.[60]

In addition to the studies that have focused on how stress affects processes such as immune surveillance that govern tumour survival, attention must also be directed at how stress affects events that modulate the development and accumulation of somatic mutations and genomic instability. Other relevant biological processes such as increases in DNA damage, alterations in DNA repair, and inhibition of apoptosis might explain the variance in disease outcomes.[24,48,61,62] After exposure to x-radiation, peripheral blood leucocytes obtained from 28 non-psychotic, non-medicated new psychiatric patients showed greater impairment of DNA repair when compared with 28 age-matched and gender-matched blood-bank controls. Patients who were more depressed showed significantly worse repair of damaged DNA than did their less depressed

counterparts.[48] Apoptosis is another important defence against the development of malignant cells by a process of genetically programmed alterations in cell structure that leads to failure of proliferation and differentiation, and eventual cell death.[62] In an study of stress, lymphocyte death was decreased during examinations compared with a lower-stress baseline after phorbol ester inhibition of radiation-induced apoptosis in peripheral blood leucocytes.[63]

Different results have been reported in studies in which DNA-repair capacity of 16 first-year and second-year medical students, assessed by a host-cell reactivation assay, was positively associated with levels of perceived stress.[62] Although these findings are in apparent contrast with the psychiatric inpatient study,[48] the authors caution that a number of important differences in methods between the two studies, such as characteristics of the populations, assays used to measure DNA repair, and the effect of acute versus chronic stress, warrant consideration and do not necessary imply that the studies contradict each other. Irrespective of the interpretation of the results, both these studies suggest that psychological factors have an effect on DNA repair.

The relation between stressful life experiences and breast cancer has been the subject of a great deal of research, most of which has been characterised by weak design and contradictory results. A retrospective study[64] did not show any important association between stressful life events and breast cancer. A meta-analysis[65] concluded that the few well-designed studies that have been done did not find evidence of a link. A further observational cohort study[66] also did not confirm that severely stressful life experiences increase the risk of relapse of breast cancer.

The role of psychological factors in cancer initiation and progression has been reviewed,[67] and, despite the availability of some prospective studies, there is no certainty about the role of any specific factor. An important reason might be that the interactions among several psychological factors, and the interactions of psychological and biomedical risk factors, have rarely been investigated. The effect of psychological factors has been shown more convincingly for cancer progression than for cancer initiation. Several features of methods used were mentioned as possible reasons for not finding the expected relations.[67] Conflicting reports on the association between tumour development and psychological stress in both human and animal studies might be explained by the variations in stress chronicity, timing of stress, and types of tumours tested.[31]

Although the published work investigating the involvement of psychosocial factors in cancer cause, progression, or response to treatment is extensive, the most common are studies comparing patients with cancer with those who do not have the disease. These studies could be flawed by the effects of patient's knowledge of their prognosis. Many of the effects of psychosocial factors are likely to be related to behavioural choices, such as smoking, that are known to affect the risk of cancer. The determination of causal links between psychosocial factors and the incidence of cancer is also obscured by the long delay between the development of malignant disease and the detection of neoplastic disease. Furthermore, the studies have used types and stages of cancer that differ biologically in important ways and therefore could be affected differentially by psychological and immune factors.[68]

Clinical implications

The determination of the role of stress in the onset and progression of cancer has faced many difficulties such as the stage of the disease and health behaviours. In addition to the direct effects of psychological states on physiological function, individuals who are stressed and depressed are more likely to have health habits that put them at great risk, including worse sleep, a greater propensity for alcohol and drug abuse, worse nutrition, and less exercise—health behaviours that have immunological and endocrinological consequences.[68] Reducing the effect of psychological stress through social support, including the presence of a social network or psychological intervention, has been shown to increase survival time and decrease the rate of metastasis.[31,67–73] Patients with metastatic breast cancer were randomly allocated to a treatment or a no-treatment control group. After the 1-year intervention, which consisted of weekly supportive group therapy with self-hypnosis for pain associated with the routine oncological care, a substantial difference was found in survival time in favour of the psychological intervention group (36·6 months) compared with the control group (18·9 months). These results were judged remarkable and clinically relevant.[71] In another study,[74] the correlation between tumour evolution and the role of depression and of the immune system was investigated in patients who had undergone surgery for mammary carcinoma. 50 patients had individual psychotherapy and psychopharmacological treatment; they showed a significantly slower evolution of the tumour and a relevant improvement from depression along with normalisation and a boost of the immune measurements compared with another randomly chosen control group of 50 patients. Patients with malignant melanoma who received group therapy showed a significant increase in lymphocytes and NK cells.[73] An assessment of recurrence and survival for 68 patients with malignant melanoma who had participated in a 6-week structured psychiatric group intervention 5–6 years earlier, shortly after their diagnosis and initial surgical treatment, showed a higher trend for recurrence (13 of 34) and a significantly higher death rate (ten of 34) in control patients than in the experimental patients (seven of 34 and three of 34, respectively). These results were not replicated in a study of supportive-expressive group therapy, which showed that psychological support does not lengthen survival in women with metastatic breast cancer, but improved mood and the perception of pain, especially in women who were initially more distressed.[75] However, the results of psychiatric interventions that enhance effective coping and reduce affective distress seem to have beneficial effects on survival, but are not proposed as an alternative or independent treatment for cancer or any other illness or disease.[73]

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Search strategy and selection criteria

The authors accessed personal collections of reprints, scanned key journals, contacted colleagues, and searched databases such as Medline, PubMed, and OVID, between 1977 and 2003, using the keywords "cytokines and brain", "cytokines and cancer", "stress hormones", "psychological stress and cancer", "depression and cancer", "psycho-neuroimmunology". Only papers published in English were selected. To simplify the review, the authors arbitrarily chose the studies, in an attempt to review the relations between stress, psychological dysfunction, endocrine function, neural function, and immune function, in order to explore the influence of different stressors on the immune response and cancer risk and progression. The authors recognize that this is a rudimentary approach, but an attempt was made to selected studies that showed clinically relevant findings and contradictory results.

Conclusion

Evidence mainly from animal models and human studies suggests that stress and depression result in an impairment of the immune response and might promote the initiation and progression of some types of cancer, mainly associated with a DNA tumour virus, retrovirus insertion near a cellular oncogene, and other viruses such as EBV. Through HPA activation, the mediators released during chronic stress suppress some non-specific and specific parts of the immune response, including NK-cell activity, phagocytosis, production of inflammatory cytokines (ie, interleukin 2, interferon γ, and TNF α by Th1 cells), and cytotoxic T-cell activity, compromising the most important effectors of the immune response against tumours. Furthermore, other relevant biological processes affected by stress, such as the increases in DNA damage, accumulation of somatic mutations, alterations in DNA repair, and inhibition of apoptosis might be involved in the onset and outcome of some types of cancer. Future research in psychoneuroimmunology will be needed to learn what pathways and circuits are involved in the relation of stressors with the HPA and the immune systems with respect to cancer onset and progression. Our growing understanding of immunomodulation and the links between the CNS, and endocrine and immune systems might improve the chances for successful psychoneuroimmunoendocrine interventions.

Conflict of interest

We declare no conflict of interest.

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