

## REVIEW ARTICLE

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# The role of depression and neuroimmune axis in the prognosis of cancer patients

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## Summary

New exciting research in psycho-oncology has shed light on the mechanisms by which biobehavioral signaling in cancer interplays with the neuroimmune axis, as well as on the progression and mortality of cancer patients.

Cancer and cancer therapy can collectively result in inflammation and cytokine production, which have been associated with occurrence of depression. Conversely, depression supports a chronic activated hypothalamopituitary-adrenal axis (HPA) and further determines cortisol and adrenal disturbances, as well as immune dysfunction and increased cytokine production. Through these processes, depression is associated with a worse cancer outcome. New treatment strategies which counter

the aberrant pathways between depression and cancer, such as drugs that target cytokines, pro-inflammatory signaling, neuroendocrine, metabolic pathways and sympathetic activation, might disrupt important vehicles for cancer progression.

In this review, we emphasize the major pathways that link inflammation, depression and immunity, in order to highlight potential therapeutic strategies which may become of paramount importance to those depressed individuals with cancer that have a higher risk for developing a more aggressive disease.

**Key words:** cancer, depression, HPA axis, inflammation, prognosis

## Introduction

The notorious expression from the ancient Latin writings, "Mens sana in corpore sano", leaves us on the horns of a dilemma when applied to the field of psycho-oncology. It is without doubt that a sick body affects the mind, cancer being one of the most relevant examples in which the entire process, from diagnosis to physical decline, has a profound impact on the psychological state of the individual. However, many unanswered questions lie in how the disease affects the mind and how the mind affects the body, in a fashion that even modifies the course of cancer.

Depression and depression symptoms, such as worrying, distractibility, poor memory, diminished interest in previously pleasurable activities, lethargy, social withdrawal, reduced body care [1], have incidence rates as high as 50% in cancer patients, depending on the cancer localization and stage [2,3]. The association between depression

and cancer is by no means incidental, as hypothesized by recent studies in psychoneuroimmunology, which discovered a link between depression, immunity and inflammation [1,4]. It has been suggested that inflammation and proinflammatory cytokines produced by the tumor and induced by associated cancer treatments may be involved in the etiology of depression. Apart from their known role in promoting angiogenesis, invasion and metastasis in cancer [5], cytokines such as tumor necrosis factor-alpha (TNF- $\alpha$ ), interleukin 6 (IL-6), interleukin 1 receptor antagonist (IL-1ra) and c-reactive protein (CRP) influence the brain through immune-brain communication pathways [6]. Conversely, depression seems to be associated with a chronic activation of the HPA axis, which modulates the function of the cellular immune response. With a disturbed immune function and an enhanced production of cytokines, a probable consequence of depression would be an increase in the potential for cancer progression [7].

Indeed, as proven by several meta-analyses and prospective clinical studies, depression is associated with increased mortality and decreased survival of cancer patients [8-11]. Based on data from 25 independent prognostic studies, mortality rates were found to be up to 25% higher in patients experiencing depressive symptoms and up to 39% higher in those diagnosed with major or minor depression [8]. A larger meta-analysis of 76 prospective studies confirmed the results prior obtained by Satin et al. and in addition concluded that depression and depressive symptoms predict mortality independent of cancer stage or site [9]. Also, an important survival advantage was noticed in non-depressed cancer patients compared to depressed cancer patients, especially in the case of metastatic breast cancer (28.5 months) [10] and advanced non-small cell lung cancer (7.2 months) [11].

In this review, we emphasize the major pathways that link inflammation - depression - immunity in order to identify potential therapeutic targets that might be of paramount importance to those depressed individuals with cancer, that have a higher risk for developing a more aggressive disease.

## **The link between depression and inflammation**

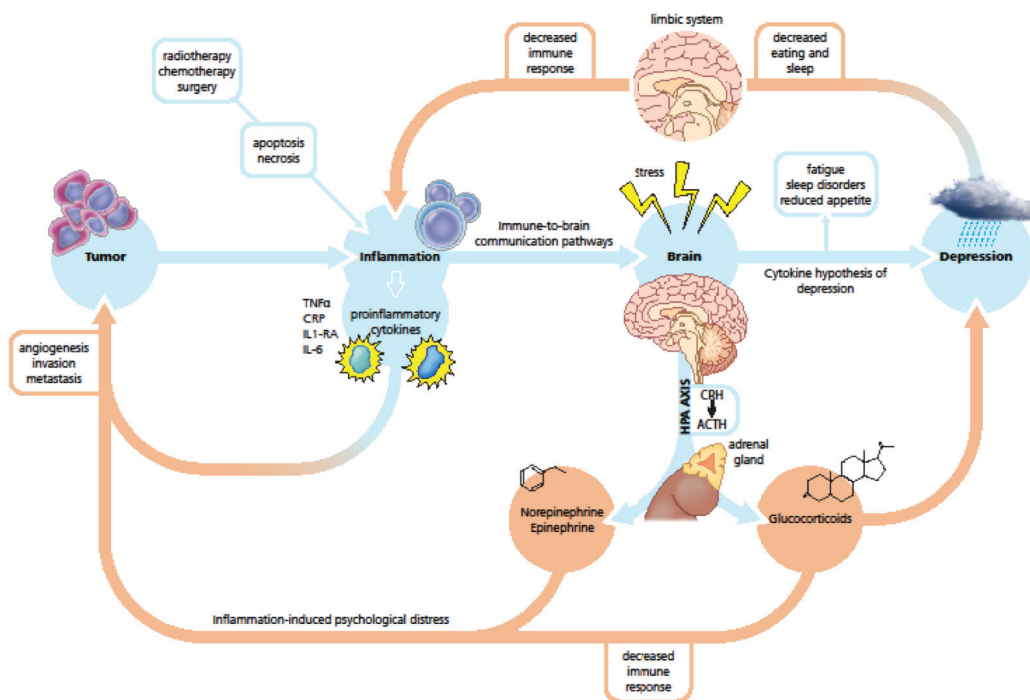
### *Cytokines trigger depression*

Cancer-associated cytokine production seems to be involved in the etiology of depression. The tumor causes an inflammatory response and the release of pro-inflammatory cytokines, such as IL-6, TNF- $\alpha$ , CRP, IL-1ra [5]. These cytokines affect the central nervous system function and promote dysregulation of the HPA axis, leading to the development of psychological symptoms, such as depression, fatigue, sleep disorders and reduced appetite [12]. Tumor-related inflammation is present early in the course of cancer; hence depression and the other psychological symptoms might also appear as early signs of cancer. Moreover, some patients develop or worsen such manifestations after the initiation of cancer treatment. A possible explanation is that cancer treatments such as surgery, chemotherapy or radiotherapy enhance the production of cytokines by adjacent non-cancer cells and immune cells recruited by the treatment-associated cell death, ultimately promoting systemic inflammation [13-15] (Figure 1A). These treatments generally result in a declining clinical state, which includes cognitive dysfunction and

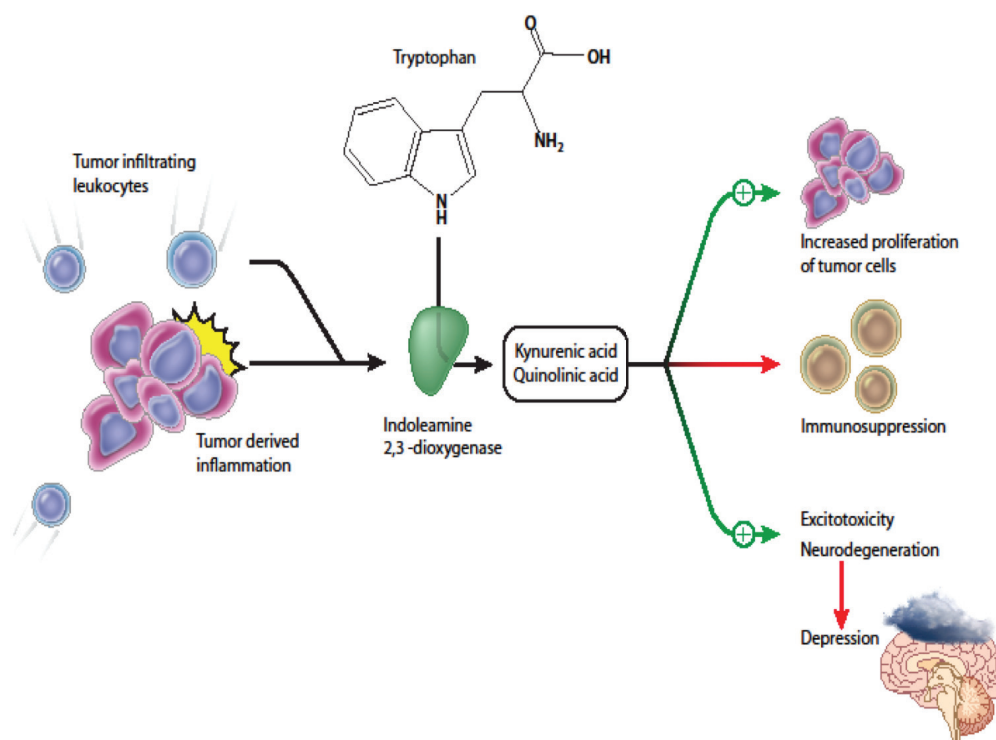
mood disorders that suddenly occur irrespective of the pretreatment state of the patient [1].

Inflammation-induced depression has been explained by the alteration of the metabolism of key molecules for the brain. For instance, inflammation leads to a disrupted tryptophan and phenylalanine metabolism through activation of indoleamine 2,3 dioxygenase (IDO), responsible for tryptophan degradation [16]. In addition, IDO has been proven to be overexpressed in various human cancers [17]. The activation of IDO leads to a decreased level of circulating tryptophan and production of neurotoxic metabolites, such as quinolinic and kynurenic acids. Quinolinic acid has been shown to act as an N-methyl dextro-aspartate receptor agonist which causes excitotoxicity associated with depression and, because it enhances lipid peroxidation and other forms of oxidative stress, it may represent a probable cause of depression-associated neurodegeneration [18]. In mouse models, experimental blockade of kynurenic acid production had led to improvement of cognitive performance when compared to wild-type animals [19]. However, recent evidence questions the kynurenine pathway as a means of tryptophan depletion in human depression [20]. Apart from their neurotoxicity, tryptophan metabolites also suppress proliferation of CD8+ tumor infiltrating lymphocytes and CD4+ T-helper 1 cells [21], which are highly important in controlling cancer cells' proliferation. Therefore, IDO might account for tumor-related immunosuppression [22]. Also, cancer treatments seem to be associated with an increase in IDO activity for some patients. In a study performed on 33 non-small cell lung cancer patients treated with multimodal combination therapy, the mean plasma kynurenine/tryptophan ratio (used as a surrogate indicator of IDO activity) was found to be increased after chemotherapy and to correlate with a worse overall survival and progression-free survival [23]. Moreover, independent of their ability to limit T-cell-mediated immune surveillance, IDO pathway metabolites led to beta-catenin activation, c-Jun N-terminal kinase signaling, reduced apoptosis and upregulation of survival, proliferation and invasion [24,25]. Therefore, blocking IDO activity might not only alleviate depressive symptoms and thus indirectly improve the evolution of cancer, but it might also have a more targeted anti-tumor effect through enhanced anti-cancer immunity or inhibition of tumor growth pathways (Figure 2).

Other types of molecules may also be involved in the disruption of neuromediator production.



**Figure 1. A** (blue): Inflammation derived from tumor behavior and treatments leads to an enhanced cytokine production, which impacts the brain through immune-brain communication pathways. The consecutive altering of brain function may subsequently induce depression. **B** (orange): Depression is associated with the chronic activation of the hypothalamopituitary-adrenal axis, which leads to increased cortisololemia. Glucocorticoids are associated with a decreased immune response, which further enhances tumor progression.



**Figure 2.** Tumor-related inflammation activates indoleamine 2,3-dioxygenase (IDO), which is responsible for tryptophan degradation into kynurenic and quinolinic acids. These metabolites induce neural excitotoxicity and neurodegeneration, which are associated with depressive symptoms. Also, IDO activation suppresses CD8+ tumor infiltrating lymphocytes and increases survival, proliferation and invasion of cancer cells.

Tetrahydrobiopterin (BH4) is a cofactor of several enzymes responsible for converting phenylalanine, tyrosine and tryptophan into functional or precursors of neurotransmitters such as serotonin, dopamine or norepinephrine [26]. However, BH4 is also a cofactor of the inducible nitric oxide synthase (iNOS), an enzyme that synthesizes nitric oxide (NO) from arginine. In depression-associated inflammation, IL-6 signaling activates iNOS. As a consequence, the amino acids meant for neurotransmitter synthesis are diverted to NO synthesis in the brain, causing a decreased production of serotonin and other transmitter molecules, which may augment existing symptoms in depressed patients. This has been proven in a study on patients with cancer, which evidenced a correlation between serum IL-2 receptor, soluble TNF- $\alpha$  receptor-2, IL-6 and phenylalanine concentration, presumably increased by lack of BH4 needed for neurotransmitter production [26].

Given the role of inflammation in the etiology of depression, several studies evaluated the effect of anti-inflammatory drugs in the treatment of depression. In a randomized controlled clinical trial performed on 40 patients suffering from an acute depressive episode, the cyclooxygenase-2 inhibitor celecoxib was proven to enhance the therapeutic action of reboxetine, a serotonin selective reuptake inhibitor (SSRI), by significantly decreasing depressive symptoms as compared to reboxetine alone [27]. Still, celecoxib's utility seems to have no benefit in treating depressive symptoms in persons older than 70 years [28]. Another option would be the use of treatments that inhibit cytokine signaling. Although anti-TNF- $\alpha$  agents were shown to improve depressive symptoms in patients with psoriasis or ankylosing spondylitis [29-31], contrasting risk-benefit ratios arose from the studies investigating TNF- $\alpha$  antagonists in association with chemotherapy in cancer patients [1]. While etanercept was reported to improve the tolerability of docetaxel, especially in terms of fatigue [32], infliximab combined with docetaxel worsened fatigue and global quality of life scores and had no effect in ameliorating anorexia/cachexia [33]. Clearly, further research is necessary to establish the risk-benefit ratio of these treatment strategies and their utility in treating inflammation-associated depression.

#### *Depression enhances cytokine production*

The link between inflammation and depression may be viewed as a feed-forward cycle, whose initiator remains highly debatable. The process

by which cytokines promote depression may be complemented by the inverse relationship, in which depression leads to increased pro-inflammatory signaling [34,35]. Elevated levels of various cytokines, such as IL-6, TNF- $\alpha$ , CRP, serum soluble interleukin-2 receptor (sIL2r) have been associated with depression [36-40]. In a study performed on 1420 young individuals, CRP levels were increased only after repeated episodes of depression [39], which further sustains the causal relationship depression-inflammation. IL-6 is the most investigated cytokine in studies that link inflammation with depressive vegetative symptoms [36,37]. Interestingly, IL-6 has been proposed as a biomarker for depression with a sensitivity of 79% and a specificity of 87% [41]. Another possible biomarker of depression might be the sIL2r, which accurately reflects T-cell-mediated immune activation due to its tight correlation with IL-2 signaling in immune cells [42]. This soluble receptor was proven to be a significant independent predictor of affective symptoms of depression, measured by the Hospital Anxiety and Depression (HAD) score [43]. Other studies also found an association between sIL2r levels and somatoform and anxiety-related somatic symptoms of depression [44]. Moreover, in patients with advanced colorectal cancer, survival proved to be shorter where sIL2r alpha and IL-6 levels were higher, whereas the ability of sIL2r alpha to predict HAD depression score was independent of survival [43].

However, the underlying mechanisms of the link between increased levels of cytokines caused by depression and their further consequences on cancer initiation and progression are highly ambiguous and are based more on hypotheses than evidence [45]. We can only speculate that depression directly influences cancer evolution. An interesting example is a study performed on parents that have been exposed to the major stressful event of losing their child. Aside from the increased cancer incidence that the bereaved parents presented compared to the non-bereaved members of the population, it has been also proven that after a follow-up period of 20 years, the bereaved parents had an increased risk of death if their cancer had been diagnosed before the tragic event, and not after [46]. Moreover, the improved cancer outcomes that resulted from the use of various psychological interventions greatly support the influence that depression might have on cancer progression [47,48].

#### **The hypothalamo-pituitary-adrenal axis**

Several multi-factorial pathways might ex-



plain why depression is associated with a worse cancer prognosis and an advanced stage disease. Apart from the evident clinical consequences of depression, such as decreased compliance to treatment or to preventive screening procedures, sleep problems and eating disorders [10,11], depression seems to be linked to a disorder of the neuroimmune system, via the chronic activation of the HPA [49] (Figure 1B).

One of the culprits involved in the interplay between psychological processes and cancer progression is cortisol. The stimulation of the HPA axis by stress elicits a response from the corticoadrenal gland and increases the glucocorticoids levels. Clinical studies confirmed that higher concentrations of cortisol were found in patients with depression at 8 AM and 8 PM [41] and observed that the higher evening cortisol levels were associated to elevations both in total depression and vegetative depression [37]. This occurrence is thought to be the result of cortisol-mediated stimulation of serotonin reuptake, a model which is consistent with the efficacy of serotonin reuptake inhibitor therapy in depressed patients [50].

Depression-associated HPA axis dysregulation was also linked to adult hippocampal neurogenesis. In a mouse model, the blockage of stem cell proliferation in the dentate gyrus led to impaired cortisol regulation [51]. The explanation may involve a member of the glucocorticoid receptor signaling pathway, the serum- and glucocorticoid-inducible kinase 1 (SGK1) whose increased expression in depression was shown to impair hippocampal neurogenesis, leading to a feed-forward cascade between depression-associated hypercortisolemia and reduced hippocampal neurogenesis [52]. This might be of particular importance, especially in patients that receive partial or fractionated whole-brain irradiation, which are at risk of developing cognitive impairment. Due to the observation that decreased hippocampal neurogenesis could be involved in the pathogenesis of radiation-induced brain injury [53,54], patients with depressive symptoms that receive brain irradiation might have a higher risk for developing cognitive impairment compared to non-depressed cancer patients.

The intuitive consequence of depression and increased cortisol secretion is a decreased immune function. In a randomized controlled trial performed on newly diagnosed breast cancer patients with depression, depression treatment with a 12-month psychological intervention was efficient by indirectly decreasing immune mark-

ers, such as white blood cell count, neutrophil count, and helper/suppressor ratio [55]. In fact, the down-regulation of the cellular immune response, represented by impaired NK cell toxicity, defective T cell production of T helper-1 vs T helper-2 cytokines and decreased T cell proliferative response to mitogens, would allow cancer cells to avoid recognition and destruction by the immune system and to further develop a more aggressive course of disease [14,56]. Support for this proposal comes from the observation that the cortisol slope and high depression scores were significantly associated with decreased survival, as proved by a prospective study including 217 patients with metastatic renal cell carcinoma [57]. In patients with non-small cell lung cancer, the lack of diurnal variation of cortisol was associated with an early mortality and low total and cytotoxic T-cell lymphocyte counts [58]. Moreover, ovarian cancer patients who had remained disease-free after 1 year were shown to display more normalized levels of cortisol [59]. The severity of cancer is linked to both cortisol levels and depressive scores, as noted in patients with advanced-stage ovarian cancer, who had greater affective and vegetative symptoms and higher cortisol areas under the curve as compared to patients with low malignant potential tumors [37].

The correlation between cortisol levels and depression has led to the proposal of cortisol variation as a biomarker of depression, obtaining a sensitivity of 81% and specificity of 88% at a cut-off value of 33.5% [41]. Further studies need to be performed in order to establish its possible prognostic role on cancer progression in depressed patients.

### **The paradoxical coexistence between inflammation and hypercortisolemia**

In depressed patients with disturbed HPA axis and increased cortisol production, cancer-related inflammation should be theoretically restrained by cortisol, due to its inhibitory effect on several inflammatory pathways [60]. Paradoxically, patients suffer a co-occurrence between increased cortisol levels and increased cytokine levels. The constant production of cytokines may be the trigger for increased glucocorticoid secretion, which causes the circadian variation profile of cortisol level to become flattened by reducing the cortisol slope variation throughout the day [41]. In turn, the glucocorticoid levels may further induce glucocorticoid resistance, which reduces negative feedback signaling and ultimately glucocorti-

coid level regulation [61]. Consequently, not only that glucocorticoids fail to inhibit inflammation, but cytokine levels continue to increase due to absence of antagonism by cortisol. This process seems to involve a glucocorticoid receptor hypoactivation [62,63].

Inflammatory cytokines and their inflammatory signaling pathways, such as nuclear factor kappa-B (NF- $\kappa$ B), signal transducer and activator of transcription (STAT) or mitogen-activated protein kinase (MAPK), may explain the hypoactivation of the glucocorticoid receptor through multiple mechanisms. For instance, members of the NF- $\kappa$ B [64] and the STAT [65] signaling pathways inhibit activated glucocorticoid receptor binding to DNA. Because the inactive glucocorticoid receptor is located in the cytoplasm, other signaling pathways, such as activated p38 MAPK [66], disrupt glucocorticoid receptor function by preventing its translocation into the nucleus. Protein kinase A (PKA), the downstream effector of cAMP-mediated extracellular signals, has been shown to potentiate the action of the glucocorticoid receptor [67] and inhibit proinflammatory signaling. As a consequence, new therapeutic strategies that either increase PKA activity or inhibit NF- $\kappa$ B, STAT and MAPK signaling might become feasible in overcoming glucocorticoid resistance, with subsequent immune function rebalancing, normalization of cortisol levels which would ultimately interrupt the feed-forward cycle between HPA axis hyperactivation and inflammation.

Moreover, independent from their implication in glucocorticoid resistance, NF- $\kappa$ B [68], STAT [69] and p38 MAPK [70] signaling pathways are activated in various types of cancer. Particularly in these tumors, targeting the overexpressed pathways in order to reverse glucocorticoid resistance might have an additional benefit of inhibiting tumor growth. However, caution must be taken in evaluating therapies that activate PKA in certain endocrine tumors, such as tumors of the pituitary, adrenal cortex and thyroid, where the cAMP/PKA pathway has been found to be involved in cancer initiation and progression [71,72].

### **The sympathetic adrenal system**

Another pathway activated by chronic stress is the sympathetic adrenal system. Cancer-related stress, such as depression, anxiety, psychological discomfort, stimulates the adrenal medulla, thereby increasing the levels of epinephrine and norepinephrine [73]. In the wake of this evidence, it was noticed that recently diagnosed cancer pa-

tients receiving beta-blockers reported less cancer-related psychological distress, in the form of intrusive thoughts [74]. Apart from increasing the heart rate and blood pressure, catecholamine hormones are able to stimulate angiogenesis through the release of vascular endothelial growth factor (VEGF), to promote invasion and metastasis via increased expression of matrix metalloproteinases, and thus to impact cancer progression [75,76].

A striking clinical application of the enhanced catecholamine secretion triggered by biobehavioral states comes from the observation that cancer patients who receive beta-blockers for other medical conditions have a longer overall survival than those without beta-blocker treatment [77]. The use of beta-blockers in cancer patients was associated with a decrease in mortality by an average of 17% across all major cancer types, as proven by the analysis of Armaiz-Pena and colleagues [78]. A possible explanation emerges from a study on breast cancer, which evidenced a sympathetically-mediated pro-metastatic phenotype switch of breast cancer cells, which was inhibited by the use of propranolol via prevention of tumor infiltration by CD11b(+)F4/80(+) macrophages [79]. Although beta-blockers have been reported to confer an increased risk of developing depression, there is uncertainty regarding the validity of this observation [80]. Thus, studies which assess the putative beneficial effects of beta-blockers in cancer treatment could clarify the safety and risk-to-benefit ratio of such therapy in cancer patients who are prone to develop depression. Apart from adrenergic receptor blockers, other drugs that prevent adrenergic signaling, such as Src family kinase inhibitors [78] or P38/MAPK inhibitors might be potent tools for inhibiting tumor progression [81]. Other notable potential targets would be the pro-inflammatory beta-adrenergically linked transcription control pathways, such as the NF- $\kappa$ B or STAT signaling systems [82,83]. As a logical consequence of the psycho-endocrinological pathways involved, the target group most likely to benefit from such interventions would be cancer patients suffering from depression or other forms of psychological distress.

### **Depression, therapeutic interventions and cancer outcomes**

The impact of depression therapy on cancer evolution has been evaluated in several studies and brought new insights into the depression-cancer outcome relationship. Spiegel analyzed randomized intervention trials with psychological in-

terventions, showing that psychological therapy was associated with increased survival in cancer patients, in the case of breast, melanoma, gastrointestinal, lymphoma and lung cancer [48]. Also, in a study conducted on 227 surgically treated breast cancer patients that were followed for 11 years, the authors noted that the psychological intervention arm of the group had a lower risk of breast cancer recurrence and a reduced risk of all-cause mortality [47]. In the same group of patients, after being diagnosed with a recurrence, some patients received psychological intervention. Notably, immune function levels were shown to be higher in the experimental arm of the study after 1 year [84]. K uchler et al. conducted an interesting randomized controlled trial which evaluated the effect of preoperative psychological intervention on the survival in patients with gastrointestinal cancers. The results showed that such preoperative psychological interventions improve the survival of patients with gastric, pancreatic, colorectal and primary liver cancers. Because other studies conducted postoperative psychological intervention on patients, the authors suggested that this may account for the observed lack of improvement in terms of survival in such studies [85].

However, other research, such as the study of Guo et al. who assayed the effect of concomitant exposure to radiotherapy and psychosocial care measures on patients, reported no significant improvement in terms of disease-free and overall survival [86]. Also, in patients with metastatic non-small-cell lung cancer, early palliation of symptoms improved depressive scores, but the observed increase in survival could not be attributed to depressive symptom treatment [87].

On the other hand, the pharmacological treatment of depression did not only fail to improve cancer outcomes, but paradoxically, it also elevated the risk for all-cause mortality and cardiovascular disease mortality in long-term breast cancer survivors [88]. The influence of pharmacological therapy is further confounded by a double-blind randomized trial in patients with advanced cancer, but without major depression, in which the SSRI inhibitor sertraline had no significant effect on depression, anxiety, fatigue or quality of life and, more importantly, had no benefit in prolonging the survival of cancer patients [89]. The lack of efficacy of the pharmacological treatments in treating depression could be explained by the

existence of a treatment resistance caused by increased inflammation [90]. Considering the inflammatory state that cancer patients develop during the course of their disease, are they less likely to respond to pharmacological treatments when compared to depressed patients without cancer? If so, would an antiinflammatory treatment potentiate the action of antidepressants in this specific group?

## Conclusions

Understanding the mechanisms by which biobehavioral signaling interplays with the neuroimmune axis and how their association results in a dismal cancer outcome, is important for establishing future directions in research.

It is not clear whether depression itself directly worsens cancer prognosis or it is rather a marker of increased inflammation and hormone levels, which further worsen cancer prognosis, particularly when depression precedes cancer diagnosis. However, treating depression might prolong the survival of cancer patients, as suggested by several studies on interventional psychotherapy. The future development of new pharmacological approaches that target the aberrant inflammatory response driven by cytokine production is worth pursuing, because the feed-forward cycle involving depression and inflammation continues to grow in importance as a vehicle for cancer progression. This loop can also be exploited to identify markers for early detection of depressed patients at high risk of a more aggressive cancer behavior that warrants specific intervention.

Considering the myriad of signaling pathways that lead to or derive from depression, several treatment strategies might be exploited. Drugs that target pathways involved in both depression and cancer progression, such as cytokines, pro-inflammatory signal transduction pathways, neuroendocrine targets, sympathetic activation and metabolic targets, might not only improve depressive symptoms, but also cancer outcomes.

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