

Biological Pathways Linking Cancer and Major Depressive Disorders

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Abstract

Cancer is widely recognized as a physical disease, but it can also have significant effects on mental health. Approximately 15-25% of cancer patients experience major depressive disorder (MDD) or clinically significant depressive symptoms. Growing evidence indicates that chronic inflammation and immune activation may contribute to cancer-related depression, although the biological mechanisms underlying this relationship are not yet fully understood. This review examines the inflammatory pathways linking cancer and depression, with a particular focus on how chronic inflammation, immune activation, inflammatory biomarkers impact brain function. Current evidence suggests that inflammatory cytokines, including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF- α), and C-reactive protein (CRP), may influence neurotransmitter signaling and contribute to depressive symptoms. However, most available evidence remains observational, making it difficult to establish a direct relationship between inflammation and depression. Overall, this review highlights chronic inflammation as a key biological mechanism that may contribute to depression in cancer patients while emphasizing the need for further research to clarify the relationship between inflammation and depressive symptoms. A better understanding of these mechanisms may improve the recognition and management of depression while guiding future research and more personalized approaches to cancer care.

Introduction

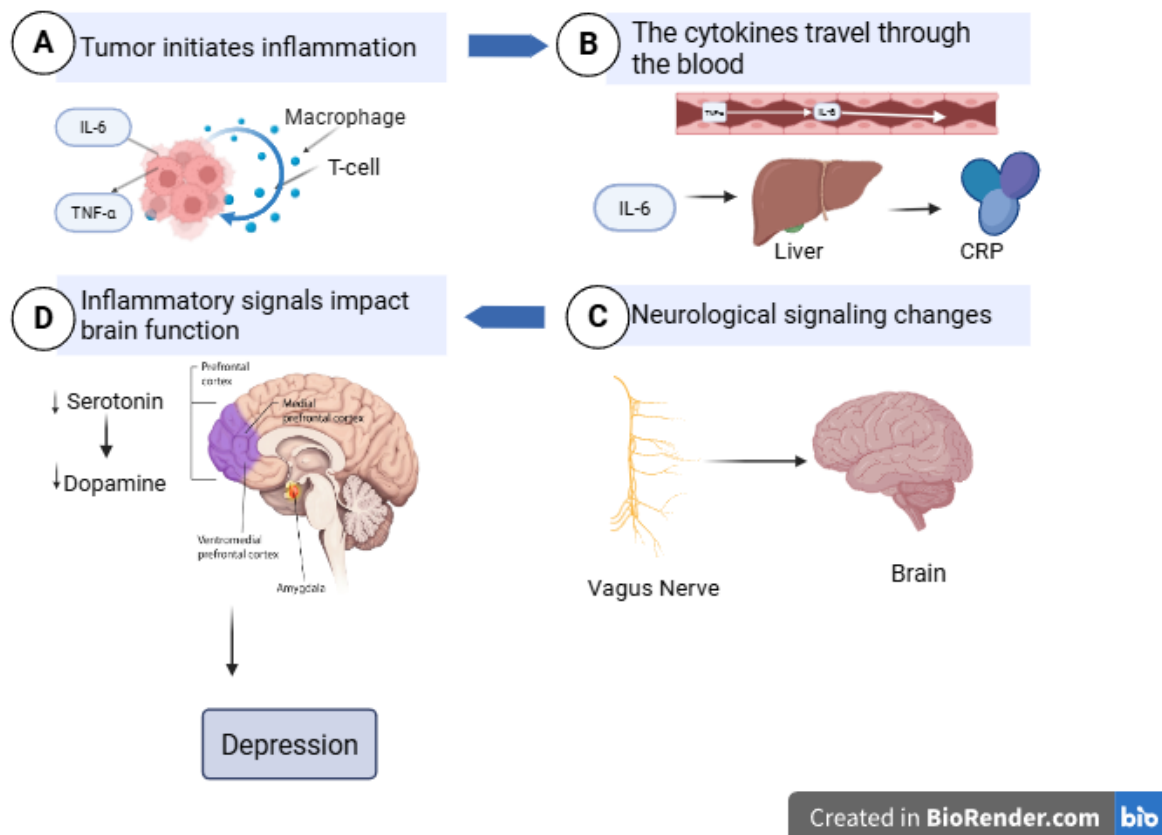
Cancer remains one of the leading causes of illness and death worldwide, affecting millions of people each year (World Health Organization, 2023). Although cancer is primarily recognized as a disease that affects the body's cells and organs, its effects on mental health are also well documented. One of the most common mental health conditions experienced by cancer patients is depression, a mood disorder characterized by persistent feelings of sadness or loss of interest that can interfere with one's daily life. Approximately 15–25% of cancer patients experience major depressive disorder (MDD) or clinically significant depressive symptoms, a prevalence markedly higher than that of the general population, where approximately 10% of adults experience major depressive disorder or clinically significant depressive symptoms in a given year (Massie, 2004; Hasin et al., 2018).

Depression is a complex disorder involving biological, psychological, and social processes. Inflammation and immune system dysregulation are increasingly recognized as major biological contributors to depressive symptoms (Miller & Raison, 2016). Depression significantly reduces quality of life and can negatively affect cancer treatment outcomes. Common symptoms include fatigue, difficulty concentrating, loss of motivation, and persistent feelings of sadness or hopelessness (National Institute of Mental Health, n.d.). Many of these symptoms overlap with symptoms commonly experienced during cancer, making diagnosis and treatment more challenging. Depression is also associated with poorer treatment adherence, as patients experiencing depressive symptoms may be less likely to attend medical appointments, follow medication schedules, or complete recommended treatment plans (Li et al., 2017). Since treatment adherence plays a critical role in cancer outcomes, understanding the mechanisms underlying cancer-related depression is essential for improving both mental health and overall cancer care.

For many years, depression in cancer patients was primarily viewed as a psychological response to illness. A cancer diagnosis often brings uncertainty, fear of disease progression, financial stress, changes in physical appearance, and anxiety about the future. Pain, intensive treatments, frequent

hospitalizations, and major lifestyle changes can create substantial emotional distress throughout the disease process. Psychological factors remain a vital component of cancer care. However, psychological stress alone doesn't fully explain the high prevalence of depression observed among cancer patients, suggesting that additional biological mechanisms may contribute to its development (McFarland et al., 2022; Miller & Raison, 2016).

Growing evidence indicates that, beyond psychological factors, biological mechanisms also contribute to cancer-related depression (Miller & Raison, 2016). One of the most widely studied biological pathways linking cancer and depression is chronic inflammation and immune activation:



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Figure 1. Proposed biological pathway linking cancer-related inflammation to depression. (A) Tumors create an inflammatory microenvironment by activating immune cells, including macrophages and T cells,

which release pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF- α). (B) Pro-inflammatory cytokines, including IL-6 and TNF- α , enter the systemic circulation. IL-6 stimulates the liver to produce C-reactive protein (CRP), a downstream marker of systemic inflammation, while TNF- α continues to promote immune activation and inflammatory signaling throughout the body. (C) Circulating inflammatory mediators, including IL-6, TNF- α , and CRP, communicate with the brain through multiple pathways, including signaling through the vagus nerve and transport across or increased permeability of the blood-brain barrier. This allows for pro-inflammatory cytokines and other inflammatory mediators produced in the peripheral immune system to influence the central nervous system. (D) Within the brain, inflammation contributes to microglial activation and disrupts neurotransmitter signaling, particularly serotonin and dopamine, in brain regions involved in mood regulation such as the prefrontal cortex, amygdala, and hippocampus. These changes ultimately contribute to the development of depressive symptoms in cancer patients.

This pathway serves as the foundation for the remainder of this review (**Figure 1**). The following sections examine the evidence supporting each stage of this proposed mechanism. The inflammatory pathway also helps explain why depression does not develop in every cancer patient. If inflammation alone caused depression, nearly all patients with elevated inflammatory markers would experience depressive symptoms. Instead, depression risk appears to depend on multiple factors, including cancer type, cancer stage, treatment status, age, sex, social support, and psychiatric history (McFarland et al., 2022). These differences suggest that inflammation is an important contributor to cancer-related depression but likely interacts with other biological, psychological, and social factors rather than acting independently.

Taken together, depression is now viewed as a biopsychosocial condition in which biological, psychological, and social factors interact to influence mental health. Chronic inflammation may increase susceptibility to depression, while psychological stress, coping ability, and social support also influence emotional responses to cancer (Miller & Raison, 2016). This review will explore the biological pathways

involved in the development of major depressive disorder (MDD) in cancer patients, with a particular focus on how chronic inflammation and inflammatory biomarkers impact brain function. Understanding these biological pathways may improve the recognition and treatment of depression while supporting cancer care.

Chronic Inflammation and Immune Activation (The Inflammatory Hypothesis of Depression)

One of the first steps linking cancer and depression is chronic inflammation. Inflammation is the body's natural response to injury, infection, and disease by promoting removal of harmful agents and tissue repair. However, unlike acute inflammation, which is a short-term protective response that typically resolves within days, chronic inflammation persists for months or even years, leading to continuous immune activation that can contribute to disease progression and disrupt normal physiological processes. Cancer is commonly associated with chronic inflammation because tumors continuously interact with the immune system, resulting in persistent immune activation (McFarland et al., 2022). As tumors grow, they release pro-inflammatory cytokines, including IL-6 and TNF- α , into the tumor microenvironment, recruiting immune cells such as macrophages, T cells, neutrophils, and dendritic cells to the site of the tumor. Activation of these immune cells stimulates cytokine release. Cytokines are essential components of the immune response, coordinating communication between immune cells while also influencing the function of other organs like the brain.

Several inflammatory cytokines, such as IL-6, TNF- α , and IFN- α , as well as other inflammatory biomarkers like CRP have been associated with depression, as illustrated in **Figure 1**. These are among the most prominent and extensively studied markers of systemic inflammation, a prolonged inflammatory response that affects the entire body rather than just a single tissue or site of injury (Haapakoski et al., 2015). Elevated levels of these molecules have been identified in many cancer patients experiencing depressive symptoms, suggesting that immune activation may influence mood (McFarland et al., 2022). Following release into the bloodstream, cytokines can communicate with the brain through several biological pathways (Miller & Raison, 2016). Some cytokines pass through specialized regions of the

blood-brain barrier (BBB), a highly selective barrier that regulates the movement of substances between the bloodstream and the brain. These specialized regions, known as circumventricular organs, naturally have a more permeable BBB, which allows inflammatory cytokines to communicate with the brain, whereas others activate the vagus nerve, a major nerve connecting the brain and internal organs that transmits inflammatory signals from the body to the brain, or stimulate microglia and astrocytes, the brain's primary immune-support cells, to produce additional inflammatory molecules (Miller & Raison, 2016). These inflammatory signals may alter neural circuits involved in emotion, motivation, and reward processing, providing a biologically plausible explanation for how immune activation can influence mood.

Serotonin and dopamine are neurotransmitters, or chemical messengers, which help nerve cells communicate. Serotonin mainly regulates mood, emotional well-being, sleep, and appetite. Dopamine, on the other hand, plays a role in motivation, reward processing, and goal-directed behavior. Research suggests that chronic inflammation can disrupt the production, release, and signaling of both neurotransmitters (Miller & Raison, 2016). One of the best-characterized mechanisms involves activation of the kynurenine pathway. Inflammatory cytokines can activate the enzyme indoleamine 2,3-dioxygenase (IDO), which moves tryptophan, the amino acid needed for serotonin production, away from making serotonin and toward kynurenine metabolism (Miller & Raison, 2016). As tryptophan levels drop, serotonin production may decline, leading to ongoing sadness and other symptoms of depression. Inflammation can also affect dopamine production and signaling, especially in the brain's reward pathways. This can result in less motivation, fatigue, anhedonia (the inability to experience pleasure), and a lack of interest in daily activities (Miller & Raison, 2016). The disruption of both serotonin and dopamine signaling offers a reasonable explanation for how chronic inflammation may lead to cancer-related depression.

Experimental Evidence Supporting the Inflammatory Hypothesis

One of the strongest sources of experimental evidence supporting the inflammatory hypothesis comes from studies examining interferon-alpha (IFN- α) therapy, an immunotherapy that was historically used to treat cancers such as melanoma and renal cell carcinoma by stimulating the immune system to attack cancer cells (Miller & Raison, 2016). Unlike observational studies, these prospective studies followed patients before and after treatment, allowing researchers to determine whether immune activation preceded the development of depressive symptoms. Across multiple studies, approximately 30–45% of patients receiving IFN- α therapy developed clinically significant depression despite having no previous history of depression (Miller & Raison, 2016). Because IFN- α directly activates the immune system before depressive symptoms emerge, these findings provide strong experimental evidence that immune activation can contribute to the development of depression. This supports the idea that inflammation itself can play a causal role in mood disturbances. These findings also encouraged researchers to investigate specific inflammatory biomarkers, particularly IL-6, TNF- α , and CRP, to better understand why some cancer patients develop depression while others do not. The following section examines the evidence linking these biomarkers to cancer-related depression.

Cellular and Molecular Markers Associated with Major Depressive Disorder

Several inflammatory biomarkers have been associated with depressive symptoms, including IL-6, TNF- α , and CRP. Although each biomarker participates in the body's inflammatory response, they differ in their biological roles and their associations with depression. The following sections examine the evidence supporting IL-6, TNF- α , and CRP as biomarkers of cancer-related depression, as well as the strengths and limitations of the current research. Better understanding of these biomarkers may improve the identification and treatment of cancer-related depression.

Interleukin-6 (IL-6)

IL-6 is one of the inflammatory biomarkers most commonly associated with depression in cancer patients. Under normal physiological conditions, IL-6 helps protect the body from infection and tissue

damage by launching a pro-inflammatory response. During cancer progression, however, excessive IL-6 production may contribute to chronic inflammation and disease progression (McFarland et al., 2022). IL-6 levels typically increase in cancer patients because tumor cells and surrounding immune cells, particularly macrophages and T cells, produce and secrete IL-6 into the tumor microenvironment (Hanahan, 2022). Cancer-related tissue damage, immune activation, and certain cancer treatments can further stimulate IL-6 production. As a result, cancer patients with advanced disease commonly exhibit elevated systemic IL-6 levels (Hanahan, 2022).

Multiple studies have demonstrated associations between elevated IL-6 levels and depressive symptoms in cancer patients. For example, Lutgendorf et al. (2008) reported that ovarian cancer patients with higher IL-6 levels experienced greater depressive symptoms and poorer quality of life. Similarly, a study found that cancer patients with higher circulating IL-6 levels experienced greater depressive symptoms, further supporting an association between inflammation and depression (Li et al., 2017). These findings suggest that IL-6 may influence mood through inflammatory pathways affecting the brain.

Despite these findings, IL-6's ability to predict depression remains uncertain. Although many studies report positive associations between elevated IL-6 levels and depressive symptoms, results are not consistent across all patient populations. Disease stage, treatment status, and cancer type all influence inflammatory activity and may contribute to differences among studies. In addition, differences in study design, methods used to measure IL-6 (such as blood serum versus plasma samples), and the depression assessment tools used (for example, clinical interviews versus self-report questionnaires) make comparisons across studies more difficult (McFarland et al., 2022). Therefore, IL-6 appears to be a meaningful biomarker of inflammation but is unlikely to predict depression in every cancer patient. Furthermore, some cancer types demonstrate greater IL-6 activity than others. Ovarian, pancreatic, and lung cancers have been associated with particularly high inflammatory activity and elevated IL-6 levels because these tumors often produce substantial amounts of inflammatory cytokines and create highly

inflammatory tumor microenvironments (Lutgendorf et al., 2008). Although IL-6 represents a key component of inflammatory signaling, it is only one component of a much broader immune response.

Tumor Necrosis Factor-Alpha (TNF- α)

TNF- α is another important pro-inflammatory cytokine that has been widely studied in both cancer and depression. Like IL-6, TNF- α is primarily produced by activated macrophages, T cells, and other immune cells within the tumor microenvironment. TNF- α plays an essential role in coordinating the immune response by promoting inflammation and helping immune cells recognize and destroy abnormal or cancerous cells through a process known as tumor surveillance. Although tumor surveillance is beneficial because it helps limit tumor growth, persistent TNF- α production can become harmful by promoting chronic inflammation and tissue damage. Similar to IL-6, elevated TNF- α levels have been associated with chronic inflammation and depressive symptoms, although the biological mechanisms through which TNF- α influences brain function appear to differ (Miller & Raison, 2016).

Interest in the relationship between TNF- α and mood disorders has increased substantially over the past several decades. Meta-analyses consistently report higher TNF- α levels in patients with major depressive disorder compared with healthy controls (Haapakoski et al., 2015). Similar findings have been reported in cancer populations. Elevated TNF- α levels were associated with more severe depressive symptoms and poorer quality of life among cancer patients (McFarland et al., 2022). These findings suggest that chronic inflammation driven by TNF- α may represent another biological mechanism linking cancer and depression.

Several biological mechanisms may explain these associations. TNF- α activates microglia, increases neuroinflammation, and increases blood-brain barrier permeability, allowing inflammatory signals to influence the central nervous system more directly. Such changes may disrupt communication between neurons while altering serotonin and dopamine signaling, two neurotransmitter systems essential for mood regulation (Miller & Raison, 2016).

TNF- α has also become a potential therapeutic target. Studies in patients with inflammatory diseases such as rheumatoid arthritis, psoriasis, and Crohn's disease have shown that TNF- α inhibitors, including infliximab and etanercept, can reduce inflammation and, in some patients with elevated inflammatory biomarkers, improve depressive symptoms (Miller & Raison, 2016). These medications are typically administered by intravenous infusion or subcutaneous injection at regular intervals depending on the specific drug and disease being treated. However, available evidence does not prove this procedure is optimal, and additional research is needed to determine whether TNF- α inhibitors are both safe and effective for treating depression in cancer patients (Miller & Raison, 2016). Today, TNF- α remains a promising but still emerging therapeutic target.

C-Reactive Protein (CRP)

Although IL-6 and TNF- α play important roles in inflammatory signaling, researchers have also investigated biomarkers that reflect overall inflammatory burden rather than directly driving inflammation. CRP is not a cytokine but instead a marker of systemic inflammation that is produced by the liver in response to inflammatory signaling. Because CRP is easily measured through routine blood testing, widespread clinical use has made CRP one of the most accessible indicators of inflammation (Osimo et al., 2020).

Elevated CRP levels have been associated with depression in both general and cancer populations, and individuals with depression frequently exhibit higher CRP concentrations than healthy controls (Haapakoski et al., 2015). Elevated CRP levels have also been reported in many cancer patients, suggesting that increased inflammatory burden may contribute to depressive symptoms (Osimo et al., 2020). Even though this association cannot reliably identify whether individuals are at a greater risk of developing depression or not, future studies should focus on how CRP could help cancer patients who may benefit from additional mental health screenings.

Despite these advantages, CRP has important limitations. CRP is a nonspecific inflammatory marker, and elevated levels may result from infections, obesity, chronic diseases, or numerous inflammatory conditions unrelated to depression. Consequently, CRP cannot identify either the source of inflammation or the underlying cause (Osimo et al., 2020). Unlike cytokines CRP does not appear to directly influence brain function but instead reflects inflammatory processes that may contribute to depressive symptoms (Osimo et al., 2020). Therefore, CRP may serve as a useful indicator of depression risk rather than a biological cause of depression.

Taken together, current evidence suggests that the inflammatory pathway is one of the strongest biological explanations for cancer-related depression (Miller & Raison, 2016). Studies have recognized associations between inflammatory biomarkers and depressive symptoms which led to proposed mechanisms that state inflammation may affect neurotransmitter function and brain activity (Miller & Raison, 2016). IL-6, TNF- α , and CRP could potentially provide different insights into how inflammation contributes to cancer-related depression. A summary of the major inflammatory biomarkers and their proposed roles in linking cancer-related inflammation to depression is provided in **Table 1** below. Combining inflammatory biomarkers with psychological and clinical assessment may improve the early identification and treatment of depression in cancer patients as research continues to advance.

Biomarker	Main cellular source	Role in cancer	Proposed link to depression	Study
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Interleukin-6 (IL-6)	Immune cells (e.g., macrophages) and tumor cells in the tumor microenvironment	Pro-inflammatory cytokine; often elevated in advanced cancer; helps drive chronic inflammation	Enters the blood, signals to the brain (blood-brain barrier regions, vagus nerve), activates microglia, and disrupts serotonin/dopamine → fatigue, low mood	Lutgendorf et al. (2008): ovarian cancer patients with higher IL-6 had more depressive symptoms
Tumor necrosis factor-alpha	Primarily macrophages and other activated	Promotes chronic inflammation and immune	Activates microglia, increases bloodbrain barrier	McFarland et al. (2022): higher TNF-α associated

(TNF- α)	immune cells	activation; contributes to tumor-associated inflammation	permeability, reduces serotonin and dopamine signaling, contributing to depressive symptoms	with greater depressive symptoms and poorer quality of life; Haapakoski et al. (2015) observed elevated TNF- α in major depressive disorder
C-reactive protein (CRP)	Liver (produced in response to IL-6 and other inflammatory cytokines)	Marker of systemic inflammation; reflects overall inflammatory burden rather than directly causing inflammation	Indicates elevated inflammatory activity that may be associated with increased depression risk, although it does not directly affect brain function	Osimo et al. (2020) observed that CRP is a useful marker of systemic inflammation but is nonspecific; Haapakoski et al. (2015) observed elevated CRP associated with depression

Interferonalpha (IFN-α)	Primarily produced by plasmacytoid dendritic cells and monocytes; also administered therapeutically as an immunotherapy	Stimulates immune activity against cancer cells and produces a strong inflammatory response	Direct immune activation can reduce serotonin availability and alter brain function, leading to depressive symptoms	Miller & Raison (2016) found that patients receiving IFN-α therapy frequently developed depression despite no prior history
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Table 1. Summary of the major inflammatory biomarkers discussed in this review and their proposed roles in linking cancer-related inflammation to depression.

Discussion

Clinical Significance

Growing evidence has changed the understanding of depression in cancer patients. Overall, the evidence reviewed supports that depression in cancer patients is influenced by biological mechanisms in addition to psychological factors. Although emotional distress remains an important contributor, chronic inflammation, immune activation, cytokine signaling, and neurotransmitter disruption are also associated with depressive symptoms. Rather than replacing psychological explanations, these biological mechanisms complement existing evidence and provide a more comprehensive understanding of cancer related depression. A better understanding of these pathways may improve the recognition, management, and treatment of depression in cancer patients while ultimately enhancing both quality of life and overall cancer outcomes. Future research should focus on validating inflammatory biomarkers in clinical settings and determining whether biomarker-guided screening or targeted anti-inflammatory interventions can improve the early identification and treatment of depression in cancer patients.

Current Evidence

Although substantial evidence supports a biological link between cancer and depression, one of the greatest challenges is determining whether inflammation contributes to depression, depression contributes to inflammation, or if both processes occur simultaneously. Most current research has identified strong associations between inflammatory biomarkers and depressive symptoms, but available evidence remains largely observational, making it difficult to establish a direct cause-and-effect relationship. As a result, inflammation is widely recognized as an important contributor to cancer-related depression, although the exact biological underpinnings remain unclear.

One strength of the current literature is the consistency of findings across multiple fields, including oncology, psychiatry, and immunology. Numerous studies have reported elevated inflammatory biomarkers in both cancer patients and individuals with depression (Haapakoski et al., 2015). Additional research has demonstrated significant associations between cytokine levels and depressive symptoms in cancer populations (McFarland et al., 2022). Furthermore, evidence from interferon-alpha therapy study provides stronger experimental support that immune activation may influence mood rather than simply result from depression (Miller & Raison, 2016). Collectively, these findings support inflammation as an important biological factor contributing to depressive symptoms.

Limitations of Current Research

Although these findings strengthen the biological basis for cancer-related depression, several important limitations must be considered when interpreting the current evidence. Most available studies are observational and only measure inflammation and depressive symptoms at a single point in time. Although such studies consistently identify associations between chronic inflammation and depression, they cannot determine which process occurs first. In addition, studies differed in the inflammatory biomarkers they measured, the timing of biomarker collection, the depression screening tools or diagnostic criteria used, and the types and stages of cancer included, making comparisons across studies

more difficult and contributing to inconsistent findings (Osimo et al., 2020). This remains one of the major challenges in research investigating inflammation and depression.

Inflammation may contribute to depression through changes in brain function and neurotransmitter activity. At the same time, depression has also been associated with increased inflammatory activity, even in individuals without cancer. This relationship represents a classic “chickenand-egg” problem because elevated inflammation may contribute to depression, while depression itself may also increase inflammatory activity. Distinguishing cause from correlation is especially difficult in cancer patients already experiencing significant physical and psychological stress. These challenges highlight the importance of considering potential confounding factors when interpreting the current evidence.

Several confounding factors may influence the relationship between inflammation and depression in cancer patients. Cancer stage represents one principal factor because advanced disease is often associated with greater inflammation, increased pain, fatigue, and emotional distress, making it difficult to determine whether depressive symptoms are primarily related to inflammation or other comorbidities. Differences in tumor biology and cancer type may contribute to variability across studies and influence findings. For example, pancreatic and lung cancers have been associated with both increased inflammatory activity and higher rates of depression than several other cancer types (McFarland et al., 2022). Patient demographics like age and sex both affect immune function, susceptibility to depression, and may also influence study outcomes. Older adults often have higher baseline levels of systemic inflammation, while women are generally at greater risk of developing depression than men, making both factors important potential confounders (Haapakoski et al., 2015). Treatment status also represents an important confounding factor because chemotherapy, radiation therapy, immunotherapy, and hormone therapy can stimulate inflammatory responses through tissue damage or immune activation. Resulting increases in cytokine levels may alter brain function and contribute to depressive symptoms independent of the underlying cancer (Hanahan, 2022). Pre-existing psychiatric disorders and other mental health

conditions may also increase the risk of depression while influencing inflammatory responses, making it difficult to separate the effects of cancer from previous mental health history.

Future Directions

Future research should prioritize longitudinal and experimental study designs. Following newly diagnosed cancer patients from diagnosis through treatment while measuring inflammatory biomarkers and depressive symptoms at multiple time points would provide a better understanding of the temporal relationship between inflammation and depression. Such studies could determine whether elevated inflammation consistently precedes depressive symptoms or whether both processes develop together over time while controlling important confounding factors, including cancer type, disease stage, treatment status, and socioeconomic status.

Future investigations should also examine whether combinations of inflammatory biomarkers provide greater predictive value than individual biomarkers alone while working toward standardized methods for measuring and determining inflammation and depression across studies. Overall, current evidence strongly supports an association between inflammation and depression in cancer patients, although a causal relationship has not yet been established. Addressing these questions may enable medical professionals to identify depression earlier, develop more effective screening strategies, clarify how standard cancer treatments influence inflammatory pathways, and ultimately guide personalized interventions that help prevent or reduce depressive symptoms in cancer patients.

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