Cancer Reports

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The Interplay of Chronic Stress and Cancer: Pathophysiology and Implications for Integrated Care

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Received: 20 June 2024 | **Revised:** 16 December 2024 | **Accepted:** 29 January 2025

Funding: The authors thank Department of Health Research for supporting our research vide grant no DHR-1534 (File Number: R.11012/04/2023-GIA/HR).

Keywords: cancer | cancer stem cells | chronic stress | counselling | depression | immune modulation | palliative care | psychiatry | psycho-oncology | psychotherapy

ABSTRACT

Background: Cancer-associated depression is a multifaceted condition that arises from the interplay of biological, psychological, and social factors in individuals diagnosed with cancer. Understanding this condition involves exploring how cancer and its treatments can precipitate depressive symptoms and the mechanisms behind this association. Chronic stress, inflammation, and immunological responses play a crucial role in the development of both cancer and depression. The objective of this review is to describe and synthesize information on the complex interactions between chronic stress, inflammation, immunological responses, and cancer development. Additionally, it aims to review existing evidence regarding mechanisms such as neurotransmitter imbalances, structural brain changes, and genetic predispositions as key contributors to depression in cancer patients.

Recent Findings: A comprehensive literature search on Cancer-associated Depression was conducted in electronic databases, including APA PsycINFO, Medline, Google Scholar, Embase, PubMed, Scopus, and Web of Science. The research focused on understanding the potential relationship between stress-induced depression and cancer by examining neurochemical, anatomical, immunological, genetic, and psychological changes. The findings revealed a compilation of both quantitative and qualitative studies on depression in cancer patients. Evidence suggested a potential link between cancer-induced stress and depression, with increased levels of proinflammatory cytokines (such as IL-6) and dysregulation of neurotransmitters, including serotonin, contributing to the onset of depression. Furthermore, studies indicated that antidepressants, along with psychological interventions, were effective in managing depression among cancer patients.

Conclusion: This narrative review provides insights into the importance of integrating oncology and mental health services to address the psychosocial needs of cancer patients. Future research should focus on the bidirectional interactions between stress and cancer, aiming to improve cancer care by incorporating mental health support. Addressing the mental health aspects of cancer treatment can significantly enhance patient outcomes and overall quality of life.

1 | Introduction

1.1 | Background and Significance

Depression, recognized as a pervasive and severe mood disorder, manifests through persistent sadness, hopelessness, and disinterest, adversely affecting one's daily life. Its complexity lies in the amalgamation of genetic, environmental, neurochemical, and physiological elements. Scientific studies have pinpointed neurotransmitter imbalances involving serotonin, norepinephrine, and dopamine, structural alterations in the brain like hippocampal shrinkage and modifications in the prefrontal cortex, and genetic factors highlighting the disorder's multifaceted genetic-environment interplay. The initial adaptive response to stressful stimuli involves the immune system, the hypothalamic–pituitary–adrenal (HPA) axis, and the sympathetic-adreno-medullar (SAM) system activation [1]. Therefore, in reaction to real or imagined risks to homeostasis, the brain circuitry of the hippocampus, amygdala, and prefrontal cortex processes information about the stressor and triggers physiological mechanisms of adaptation mediated primarily by catecholamines and glucocorticoids [2]. By controlling glucocorticoid secretion, the HPA axis, in addition to the autonomic nervous system, is a major component of the stress response. The hypothalamic release of corticotropin-releasing hormone (CRH) is a characteristic of this HPA-mediated stress response. CRH acts on the anterior pituitary to stimulate the secretion of adrenocorticotropic hormone (ACTH), which in turn causes the adrenals to secrete cortisol (humans) or corticosterone (rodents). When the HPA axis and SAM system are activated together, more glucose is broken down and energy is redistributed throughout a variety of tissues and organs, including the brain [1]. According to recent research, different brain areas regulate the immune system by driving a particular leukocyte trafficking pattern during periods of acute psychological stress [3]. The degree and duration of the stressor significantly impact the modification of immune function due to stress [4].

These insights from comprehensive research illustrate depression as a disorder influenced by a spectrum of neurochemical, genetic, and inflammatory factors [5–11]. The correlation between depression and cancer is significant, with heightened instances of depression and anxiety noted among cancer patients. Chronic stress exposure frequently results in severe immunosuppression, a reduction in the number and function of immune cells, and an imbalance in the ratio of Type 1 to Type 2 cytokines. Immune malfunction brought on by stress has a role in the persistent low-grade inflammation that is intimately linked to common chronic illnesses like cancer. However, cancer leads to an inflammatory environment that manifests systemically [12], which modifies the activation of the HPA axis and the proper secretion of cortisol in response to stress [13]. The perception that depression is a normal and universal reaction to serious illnesses has led to the underdiagnosis and undertreatment of depression in cancer patients complicating treatment, recovery, and overall quality of life [14–20].

1.2 | Scope of the Review

This review delves into the intricate dynamics between chronic stress, inflammation, and cancer, highlighting shared pathways that underlie these conditions. Chronic stress and cancer induce a systemic pro-inflammatory state through common signaling pathways such as NF-kB, STAT3, and mTOR, promoting tumor growth and metastasis while also contributing to neuroinflammation [21]. The reciprocal relationship between stress and cancer is evident in their mutual promotion of neuroinflammation, involving monocyte trafficking, microglial activation, and blood–brain barrier disruptions. Cancer stem cells (CSCs) are a subset of cancer cells capable of driving tumor growth, metastasis, and therapeutic resistance [22–24]. Emerging evidence suggests a complex interplay between chronic psychological stress, neuroinflammation, and the maintenance of CSC stemness [25–27]. This relationship may contribute to cancer progression, emphasizing the importance of addressing both physical and mental health aspects in cancer care.

Addressing the mental well-being of cancer patients therefore is a pressing global healthcare challenge. This underscores the importance of a holistic approach to cancer care, integrating mental health considerations. As attention shifts toward cancer recurrence surveillance, concerns arise regarding potential oversight of long-term effects on both mental and physical health [28]. This review emphasizes the necessity for further research to understand the bi-directional relationship between stress and cancer, aiming to enhance cancer care by integrating mental health support. It delves into survivors mental health challenges, offering solutions and insights into areas for future research, like precision medicine's potential for stress-reducing cancer treatments. Additionally, it identifies gaps in cancer care and anticipates future advancements in tailored, holistic care, boosting emotional and physical well-being, and increasing survivor quality of life.

2 | Understanding Depression in Cancer Patients

2.1 | Prevalence and Impact

Stress, a ubiquitous aspect of human experience, arises from a complex interplay of psychological, mental, physical, and emotional factors. Individuals are exposed to stress from daily responsibilities, occupational demands, interpersonal relationships, and external circumstances such as adverse childhood experiences, environmental toxins, socioeconomic disparities, and discrimination, all of which can significantly impact their overall well-being [29]. Further, chronic stress characterized by prolonged exposure to stressors and associated allostatic load (AL) has been shown to have deleterious effects on health, including increased risk of insomnia, gastrointestinal disorders, anxiety, depression, and cardiovascular disease [30–35]. Furthermore, they can disrupt the balance of the neuroendocrine-immune system, contributing to the development and progression of cancer [36–38]. For example, using AL as a stress marker, recent studies have found that women with high AL had a 64% increased risk of cancer [39].

2.2 | Factors Contributing to Depression in Cancer

Depression in cancer patients is an intricate and multifaceted issue that is influenced by various factors. Such individuals

TABLE 1 | Factors that may contribute to depression among cancer patients [40].

Individual characteristics	Psychological factors	Social factors	Cancer-specific factors
Age	Emotional distress	Educational level	Type of cancer
Gender	Coping behavior	Employment status	Diagnosis experience
Ethnicity	Denial	Type of occupation	Symptoms
Sexuality	Anger	Household income and wealth	Stage
Religion	Fear	Family	Grade
Disability	Grief	Social support	Prognosis
Marital status	Resilience	Belief system	Curability
	Sensitivity to others	Healthcare system	Recurrence
	Self/body Image issues	Access to care	Functional deterioration
		Welfare system	Impairment

Biological factors	Prior psychological factors	Lifestyle factors	Treatment factors
Genetic susceptibility	Personality (e.g., Type C, Type D, neuroticism)	Consumption of tabacco, alcohol, drugs	Setting (inpatient, outpatient)
Neurochemical changes	History of psychiatric disorder	Diet	Length and burden
Hormonal changes (e.g., cortisol)	Previous suicidal behavior	Obesity	Phase (e.g., acute, palliative)
Chronic pain	Prior traumatic event/abuse	Physical activity	Treatment modality (e.g., surgery, chemotherapy, radiotherapy)
Immune system functioning		Sleep	Dose
Co-morbid health conditions (e.g., Infections, neurological disorders, cardiac and respiratory disorders)		Stress	Side effects
			Long-term complications (fatigue, cognitive changes, secondary cancers)
			Cost of treatment
			Response to treatment

diagnosed with cancer have a high probability of suffering from anxiety and depression, which comes from the interaction of numerous biological, psychological, and social factors [40] (Summarized in Table 1).

2.2.1 | Individual Factors

An array of characteristics such as age, gender, ethnicity, sexuality, religion, disability, and marital status, possibly play a role in the development of depression in this population [40]. As age is a major predictor, elderly people are more susceptible to depressive symptoms owing to various factors like comorbidities and physical health decline [41]. Conversely, younger patients often experience a high level of psychological distress as their life planning and career events are disrupted [42]. Research into gender differences indicates that women are more likely to suffer depression after cancer diagnosis compared with men, due to biological influences including hormonal changes as well as differing coping mechanisms [43]. For men, however, the underreporting of emotional distress might lead to an underestimation of the prevalence of depression in this population [44]. Ethnic studies have shown that minority groups often face barriers due to stigma or systemic inequalities [45]. Religion has been shown to provide a level of solace, but also to imply guilt and conflict regarding illness about religious beliefs [46]. Sexuality is also a significant variable, as cancer survivors who are LGBTQ+ may experience heightened psychological distress as a result of stigma or lack of targeted healthcare services [47]. Disabilities can make physical and psychological challenges worse in cancer, reducing self-efficacy and fostering feelings of isolation [48]. In addition, marriage has a significant impact on mental health; married persons generally record fewer depressive symptoms owing to the intimacy of their marriage, while single or widowed patients can exhibit higher levels of loneliness and isolation [49]. These interrelated variables indicate a need for culturally adapted interventions in comprehensive cancer care.

2.2.2 | Biological Factors

Biological factors contribute to depression through inflammation, HPA axis, glutamate excitotoxicity, and genetic predisposition like 5-HTTLPR and MAOA genes [50]. Other genetic factors like 5-HTTLPR and MAOA polymorphism increase the risk of depression by altering the serotonin levels and stress response pathways [51, 52]. Neurochemical imbalances are known to be the main cause of depression, which includes low levels of serotonin, norepinephrine, and dopamine [5, 6, 53]. Hormonal changes especially those caused by cancer treatments like endocrine therapies for breast or prostate cancer are also significant contributors to depression. These therapies affect the levels of estrogen, testosterone, and cortisol which disrupt the neurochemical balance and leads to mood dysregulation [54]. Elevated proinflammatory cytokines like IL-6 and TNF-α are associated with depression in

cancer patients [8, 55]. Cancer-related pain is strongly associated with depression and emotional distress [56].

2.2.3 | Psychological Factors

Research studies show emotional distress, including anger, fear, grief, and body image issues as highly relevant contributors to depression in cancer patients [57, 58]. Many studies have showed that higher levels of distress, notably anger and fear, were associated with elevated symptoms of depression among cancer patients [40, 59]. The studies also showed that problems relating to body image were correlated with a higher incidence of depression among women with breast cancer [60]. Grieving and loss, in studies, have been associated intensely with the mental health of cancer patients, and it has been suggested that unresolved grief can heighten an individual's risk for depression [61]. Factors such as coping behaviors, resilience, sensitivity to others, and self-image have a huge impact on the development of depression among patients [62–65]. Bad forms of coping like avoidance and denial can serve to exacerbate distress, while good types like problem-focused coping can help diminish depressive symptoms [66]. Resilience, or the ability to bounce back from adversity, varies in extent among individual patients and is negatively correlated with the severity of depression [67]. Greater sensitivity to others, including fear of burdening loved ones, can magnify feelings of guilt and loneliness [49]. Moreover, changing self-image because of a physical altercation, for example, loss of hair or disfigurement can also have secondary effects on emotional well-being and depressive symptoms [68].

2.2.4 | Prior Psychological Factors

Personality traits such as Type C (characterized by suppression of emotions and excessive agreeableness) and Type D (distress-prone) are associated with higher psychological distress and poorer coping mechanisms [42, 69, 70]. Neuroticism, marked by emotional instability, predisposes individuals to heightened vulnerability to stress and negative affect [71]. A history of psychiatric illness or previous suicidal behavior further increases the risk of depression, as these individuals often have impaired emotional resilience [17, 72–74]. Moreover, prior traumatic events or abuse can lead to chronic stress responses and maladaptive coping, making such individuals more susceptible to depression during the cancer journey [75, 76]. These factors highlight the necessity of comprehensive psychological screening in cancer care.

2.2.5 | Social Factors

Social factors significantly contribute to the development and severity of depression in individuals with cancer, underscoring the complex interplay between social determinants of health and mental well-being. Educational level often influences health literacy, impacting a patient's understanding of their diagnosis and treatment, which may heighten distress [77, 78]. Employment status and type of occupation are critical, as job loss or inability to work due to cancer can lead to financial strain and reduced self-esteem, exacerbating depressive symptoms [79, 80]. Similarly, household income and access to welfare systems determine the availability of resources for coping with illness, while inadequate financial means increase vulnerability to psychological distress [81]. Family type and social support are pivotal; individuals with supportive family structures report lower depression levels compared to those in isolated or strained relationships [82, 83]. Cultural belief systems and access to care also play a role, influencing attitudes toward treatment and the likelihood of seeking psychological help [84]. Together, these factors create a multifaceted framework that shapes the mental health outcomes of cancer patients.

Socioeconomic status (SES) further compounds the risk of depression among cancer patients. Low SES, often characterized by unemployment, limited educational attainment, and financial strain, can intensify stress levels, reduce access to healthcare, and hinder the ability to seek adequate psychosocial support [85]. Social support, or the lack thereof, is a critical protective factor. Patients with limited social networks or those experiencing social isolation are more susceptible to feelings of hopelessness and depression [86].

2.2.6 | Lifestyle Factor

Depression risk in cancer patients may be attributed to a variety of lifestyle and environmental factors, such as substance abuse, diet, obesity, exercise, sleep, and stress. Cancer patients consuming tobacco, alcohol, and drugs remain at an elevated risk of mood disorders such as depression [87, 88]. Such substances can worsen psychological distress, render inadequate coping strategies, and compromise treatment outcomes. A poor diet with a deficit of dietary nutrients creates adverse effects on brain chemistry and makes individuals more vulnerable to depression through their interference with metabolic and inflammatory pathways [89, 90]. Similarly, obesity also promotes increased levels of inflammation and creates hormonal imbalances, affecting mood regulation and causing depression [91, 92]. Besides, insufficient physical activity might worsen the development of depression by limiting the benefits of exercise, which might produce endorphins and serotonin contributing to mood regulation [93]. Sleep disturbances in cancer patients may also serve as a significant risk factor since poor sleep quality and quantity are strongly associated with more severe depressive symptoms [94, 95]. Finally, chronic stress in cancer, especially upon diagnosis and treatment, plays a vital role in depression by altering physiology within the brain that amplifies emotional distress [96].

2.2.7 | Cancer-Specific Factors

Among cancer-related factors, those related to specific characteristics of cancer make a profound impact on depression development because cancer affects the physical, emotional, and social aspects. The type of cancer can have an influence on mental well-being as certain cancers like the brain or pancreas have a more unfavorable prognosis and generate profound psychological distress [97]. The diagnosis of cancer experience itself evokes fear, uncertainty, stigma, and acute

stress, often resulting in depression [98]. Research studies show Permanent pain, fatigue, or deformity worsens the state of distress [40]. The stage and grade of a cancer are associated with the severity of depression, more specifically the level of hopefulness that it provides and its mental health outcome [99]. Similarly, prognosis and curability influence the patient's outlook on life; a poor prognosis may foster hopelessness [94]. Recurrence stops being another tear in an emotional curtain and, instead, manifests itself in fear and psychological distress [100]. Functional decline together with imposed physical limitations owing to cancer or treatment could lead to a loss of independence and quality of life, thus exacerbating depression [101]. An understanding of this multifaceted set of factors and their relation to depression is critical for a holistic approach to cancer patients.

2.2.8 | Treatment Factors

The nature of the cancer is a key determinant, with certain cancers associated with poorer prognosis, including lung and pancreatic cancers, being more strongly correlated with higher levels of depression [102]. In addition, the treatment setting-inpatient versus outpatient-might influence psychological well-being. Inpatient settings, in general, are often associated with more intensive care, leading to possible increased feelings of isolation and anxiety [103]. Hence, the duration of treatment and the burden of treatment may also lead to depression since long therapies may cause chronic distress than effective treatments due to their toll, both physically and emotionally [83]. Experimental studies indicate that longer treatment intervention with either chemotherapy or radiotherapy is associated with other possible factors associated with increased risk for depression, especially when side effects like fatigue, cognitive impairment, and nausea arise [104]. The phase of the disease is an important factor, as such patients may experience more emotional distress in acute or palliative phases due to uncertainties concerning prognosis and severity of symptoms [98]. The financial burden of cancer treatment also links with depression through the added economic strain consequent to high treatment costs and subsequent feelings of helplessness and anxiety [105]. Finally, the treatment outcome represents an important variable. Poor behavioral outcomes following chemotherapy were associated with severe depression, as patients who responded poorly to cancer therapies exhibited significantly higher depression scores compared to those with positive therapeutic outcomes [106].

2.3 | Psychobiological Underpinnings of Depression in Cancer Patients

Depression in cancer patients is a complex phenomenon influenced by various psychobiological factors. Understanding the neurobiological, immunological, genetic, and epigenetic aspects of depression in this population is crucial for developing effective interventions. This section explores the psychobiological underpinnings of depression in cancer patients, focusing on neurobiological factors such as neurotransmitter dysregulation and HPA axis dysfunction, immunological factors including inflammatory responses and immune system modulation, as well as genetic and epigenetic influences.

2.3.1 | Neurobiological Factors

2.3.1.1 | Neurotransmitter Dysregulation. Neurotransmitter dysregulation, particularly involving serotonin, norepinephrine, and dopamine, plays a significant role in the development of depression in cancer patients. Serotonin imbalance, often referred to as the “feel-good” neurotransmitter, is a well-documented contributor to depression [5]. Similarly, alterations in norepinephrine and dopamine levels have been implicated in mood disorders [6]. Under chronic stress, region-specific neuronal remodeling occurs in brain areas such as the hippocampus, amygdala, and prefrontal cortex [107]. Chronic stress leads to sustained synaptic plasticity in the prefrontal cortex and induces varying dendritic changes in the amygdala and hippocampal neurons [108]. Dysregulation of these neurotransmitters disrupts mood regulation and emotional processing, contributing to depressive symptoms among cancer patients.

2.3.1.2 | HPA Axis Dysfunction. Repeated exposure to stressors increases hypothalamic CRH gene and protein expression, enhancing cellular excitability by increasing the density of catecholaminergic and glutamatergic terminals on CRH neurons. This leads to chronic HPA axis activation, resulting in glucocorticoid hypersecretion and sensitized stress responses [109]. In addition to prolonged HPA axis activation, chronic stress alters locus coeruleus-norepinephrine function, with growing evidence suggesting that increased sympathetic activity also contributes to glucocorticoid hypersecretion following chronic stress [110]. Chronic stress associated with cancer diagnosis and treatment can lead to dysregulation of the HPA axis, resulting in elevated cortisol levels [9]. High cortisol levels have been linked to depressive symptoms and impaired mood regulation in cancer patients, highlighting the role of HPA axis dysfunction in depression pathogenesis.

2.3.2 | Immunological Factors

2.3.2.1 | Inflammatory Responses. Inflammatory responses, characterized by elevated levels of proinflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), have been implicated in the development of depression in cancer patients [8]. It is widely acknowledged that both Androgen Deprivation Therapy (ADT) and second-generation anti-androgens, used to treat prostate cancer, are linked to a higher risk of depression and anxiety [111–113]. In a landmark study encompassing 37 388 prostate cancer patients undergoing ADT, 10.6% were diagnosed with depression or anxiety [112]. Despite these findings, recent studies have shown that an elevated level of IL-6, related to ADT treatment for prostate cancer, is associated with increased fatigue but not with depressive symptoms [114]. This evidence supports the idea that cancer patients experiencing fatigue, anxiety, and depression may have elevated levels of circulating inflammation markers, such as interleukin-6 (IL-6) and C-reactive protein (CRP) [115–118]. Furthermore, administering cytokines, which are involved in triggering the inflammatory response, can lead to symptoms of fatigue and depression in both humans and animals [119]. Clinical studies have revealed that roughly 30% to 45% of patients undergoing IFN-α therapy experience depression during

treatment including that of cancer [120, 121]. A double-blind, placebo-controlled study of patients undergoing IFN-α therapy for malignant melanoma demonstrated that pretreatment with the antidepressant paroxetine was effective in preventing the development of major depression and was linked to improved adherence to IFN-α therapy [120]. Chronic inflammation, triggered by cancer-related factors and treatment modalities, can hence disrupt neurobiological pathways involved in mood regulation and contribute to depressive symptoms.

The occurrence of depression in patients with glioma and the ability of inflammatory cytokines to predict it was investigated by Li et al. Among 203 patients with glioma, 66.5% showed depressive symptoms. Proinflammatory cytokines, including interleukin (IL)-6 and tumor necrosis factor (TNF)-α, demonstrated good performance in accurately predicting depression in these patients [122]. These inflammatory cytokines have potential to be effective clinical screening and diagnostic tools, as well as biomarkers for depression in patients with glioma. Another study examined the prediction ability of various circulating cytokines for depression in patients with breast cancer not receiving adjuvant chemotherapy. The researchers found that the proinflammatory cytokine IL-2 and the anti-inflammatory cytokine IL-5 demonstrated good predictability for depression, even after controlling for covariates. IL-2 had the best prediction ability among the cytokines studied, with a sensitivity of 86.7% and a specificity of 52.9% at an optimal cut-off value of 1.06 pg/mL. The findings suggest that circulating cytokines may be a valid laboratory diagnostic tool for depression in cancer patients [123].

Moreover, inflammation-induced alterations in neurotransmitter metabolism and synaptic plasticity may further exacerbate depression in this population [124].

2.3.2.2 | Immune System Modulation. Immune system modulation, including changes in immune cell function and activity, has been associated with depression in cancer patients. Dysregulation of immune responses, characterized by altered cytokine profiles and immune cell activation, may contribute to the pathophysiology of depression in this population [124]. The neuroendocrine system, particularly the hypothalamic–pituitary–adrenal (HPA) axis, plays a crucial role in the connection between immune dysregulation and depression in cancer patients [96, 125, 126].

The HPA axis is a key component of the stress response system. When the body encounters stressors, the hypothalamus releases corticotropin-releasing hormone (CRH), which stimulates the pituitary gland to secrete adrenocorticotropic hormone (ACTH). ACTH then triggers the adrenal glands to produce glucocorticoids, such as cortisol, which help the body respond to stress [127]. In cancer patients, pro-inflammatory cytokines released by the tumor or as a result of cancer treatments can overstimulate the HPA axis, leading to chronic hyperactivity [128, 129]. This disrupts the normal negative feedback loop, where glucocorticoids inhibit the production of inflammatory mediators. Instead, the immune system develops a resistance to glucocorticoids, resulting in a paradoxical co-existence of high levels of inflammatory cytokines and glucocorticoids. This dysregulation of the HPA axis and immune system can contribute to the development of depression in cancer patients [130]. In summary, the neuroendocrine system, particularly the HPA axis, plays a crucial role in the bidirectional relationship between inflammation and depression in cancer patients [128, 129]. As such, chronic activation of the HPA axis due to immune dysregulation is a key mechanism underlying the increased incidence of depression in this population. Further, the relationship between immune dysregulation, major depression, and cancer has been the subject of extensive research [131–133]. Evidence suggests that depression is associated with immune dysregulation, including changes in leucocyte trafficking, lymphocyte function, and markers of immune activation [131, 132]. Major depression has been linked to a threefold higher rate of depression in cancer patients, influencing cancer risk and survival [131, 133, 134]. A study examined the association between depressive symptoms and systemic inflammation biomarkers in patients with advanced non-small cell lung cancer (NSCLC). The researchers found that higher neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), as well as lower advanced lung cancer inflammation index (ALI), were predictive of worse overall survival in NSCLC patients. Importantly, the study also showed that patients with moderate to severe depressive symptoms were 2 to 3 times more likely to have these prognostically poor biomarker levels, even after adjusting for other factors. These findings suggest that depression may contribute to the inflammatory dysregulation already present in advanced NSCLC, potentially impacting treatment responses and survival [134]. Further research is needed to understand the biobehavioral mechanisms by which depression may influence disease progression in NSCLC.

Additionally, dysregulation of inflammatory and immune pathways in both depression and cancer has been observed, with evidence of increased expression of proinflammatory cytokines and reductions in immune cell activity [131]. A review by Barreto et al. illustrated and provided evidence of the potential role of tryptophan catabolites (TRYCATs) along the indoleamine 2,3-dioxygenase (IDO) pathway as a biological link between depression and cancer. Both depression and cancer are associated with dysregulation of inflammatory and immune pathways. IDO, the rate-limiting enzyme of the TRYCAT pathway, is induced by pro-inflammatory cytokines and catabolizes tryptophan, producing neuroactive and immune-modulating compounds. Increased IDO activity in tumor microenvironments is linked to tumor cell escape from immune surveillance. and could be a potential pharmacological target for treating comorbid depression and cancer [135]. Furthermore, the gut microbiome has been implicated in the relationship between cancer symptoms and immune function, specifically in relation to "psychoneurological" symptoms such as depression [133, 136, 137]. Overall, all these researches suggests complex and bidirectional relationships between immune dysregulation, depression, and cancer, emphasizing the need for further investigation into the underlying mechanisms and potential interventions [131–133].

2.3.3 | Genetic and Epigenetic Influences

2.3.3.1 | Genetic Markers Associated With Depression in Cancer. Genetic factors play a significant role

in the susceptibility to depression among cancer patients. Genome-wide association studies (GWAS) have identified several genetic variants associated with an increased risk of depression [11].

Several genetic polymorphisms, such as the serotonin transporter-related promoter region (5-HTTLPR polymorphism), have been linked to a higher vulnerability for mental disorders and personality traits such as neuroticism in cancer patients [138–140]. Additionally, the dysbindin gene (DTNBP1) has shown significant association with antidepressant response in patients with major depressive disorder [140, 141]. Research also suggests that mitochondrial DNA and copy number alterations in certain genes, such as EGFR and TYMS, may be associated with depressive symptoms and treatment failure in certain cancers [142, 143]. The identification of genetic markers associated with depression in cancer holds promise for personalized psychiatric interventions and improved patient outcomes [138, 139].

2.3.3.2 | Epigenetic Modifications and Their Impact on Depression. Epigenetic modifications, such as DNA methylation and histone acetylation, can regulate gene expression patterns implicated in depression pathogenesis among cancer patients. Stress-related epigenetic changes without altering the DNA sequence (including DNA methylation, histone modification, chromatin reprogramming, and non-coding RNA change) may alter the expression of genes involved in neurotransmitter metabolism, stress response, and inflammatory pathways, contributing to the development of depression [144–146].

Research has shown a strong association between epigenetic modifications and depression in cancer patients [147–151]. Epigenetic aberrations, including DNA methylation and histone modifications, are linked to the pathogenesis of depression and cancer [149–154]. Chronic stress and inflammation induce DNA methylation and histone modifications in brain regions, contributing to neurodegenerative disorders and compromised neuroendocrine-immune-metabolic adaptive systems [150, 155, 156]. The brain-derived neurotrophic factor (BDNF) gene, influenced by DNA methylation and genetic profiles, has been independently linked to suicidal ideation in patients with breast cancer [140]. Additionally, environmental factors such as prenatal depression or anxiety, malnutrition, smoking exposure, and psychological stress induce epigenetic changes, which can lead to adverse health effects like depression [150, 156–158].

A study conducted by Pu et al. explored the link between chronic stress, epigenetic modifications of Hypocretin (HCRT), and depression in cancer progression. Rats exposed to chronic stress exhibited depressive-like behaviors and had higher tumor loads. HCRT expression was found to be downregulated and its promoter hyper-methylated in depressed rats. These findings suggest that chronic stress can promote tumorigenesis and cancer progression through epigenetic mechanisms involving HCRT downregulation [159]. Exposure to stress hormones can induce epigenetic modifications that alter the expression of oncogenes and tumor suppressor genes. Research has found that a particular microRNA (miRNA-145) helps cervical cancer cells resist chemotherapy treatment. Stress hormones like cortisol can reduce the amount of miRNA-145 in cervical cancer cells infected with HPV [160]. In women with ductal carcinoma in situ, elevated stress levels were correlated with lower histone acetylation in lymphocytes, potentially contributing to a greater risk of tumor spread [161]. Chronic stress was reported to trigger an upregulation of lysine-specific demethylase 5 (KDM5A), a protein involved in modifying DNA in low-oxygen environments, thereby promoting tumor progression [162]. While significant advancements have been made in cancer treatment, the development of drug resistance remains a major obstacle. Research indicates that chronic stress may contribute to this resistance by passing down epigenetic changes through generations of cells [163]. Understanding the interplay between epigenetic modifications and depression in cancer may provide insights into potential therapeutic strategies for addressing the mental health challenges faced by cancer patients [149, 151, 155].

3 | Interplay Between Depression and Cancer

3.1 | Bidirectional Relationship

Variations in depression or chronic stress prevalence are apparent among different cancer types, with higher rates observed in oropharyngeal, pancreatic, breast, and lung cancers, while colon, gynecological cancers, and lymphoma show relatively lower rates [99].

Chronic stress affects the brain and body's neuroendocrine systems, causing changes in synaptic plasticity, dendritic structure, and the activity of the HPA axis [107, 109, 164]. Through continuous catecholamine release, monocytes from the spleen and bone marrow are drawn to the brain by chronic stress, where they migrate and take on a hyperinflammatory condition [124, 165, 166]. Chronic stress and cancer lead to the activation of specific brain regions by microglia, altering the cerebral microenvironment and reinforcing the neurocircuitry associated with stress [167–170]. Such physiological alterations may play a role in the onset and progression of cancer by inducing DNA damage, inhibiting tumor suppressor proteins, and encouraging the proliferation of cancer cells [171–173].

Additionally, chronic stress modifies the tumor microenvironment (TME), stimulating angiogenesis, tumor growth, and malignancy. It also impacts immune cell dynamics within the tumor vicinity, disrupting hematopoietic balance and impairing both innate and adaptive immune defenses, thereby facilitating cancer progression [124, 174, 175]. Within the stress signaling network, endoplasmic reticulum (ER) stress emerges as a crucial regulator of CSCs [176]. Chronic psychological stress triggers ER stress, potentially disrupting the connection between cancer stemness and stress [26, 177–179]. Specifically, chronic stress was found to stimulate lactate production in breast cancer by elevating lactate dehydrogenase A (LDHA). This increased lactate production lowered pH levels, which stabilizes the Myc protein, thereby promoting stem-like properties in breast cancer cells. One of the symptoms of long-term psychological stress is elevated plasma glucocorticoid levels [26]. According to related research, cancer patients' increased levels of glucocorticoids may mediate the release of inflammatory factors and tumor immunosurveillance, which in

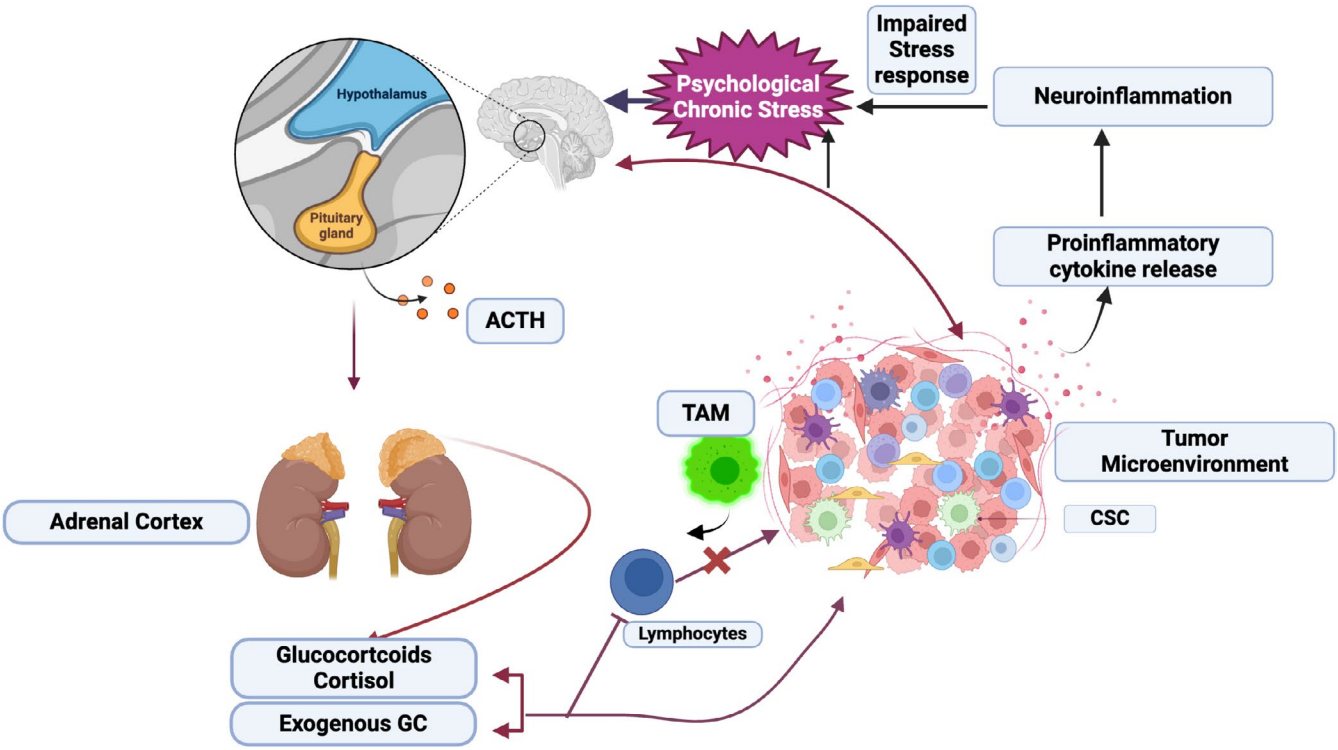

FIGURE 1 | The reciprocal association between cancer and prolonged stress: Hypothalamus-pituitary–adrenal (HPA) axis is chronically activated in response to chronic stress. Stress hormones can stimulate CSCs by promoting carcinogenesis, supporting the growth and/or progression of cancer, and regulating the microenvironment surrounding tumors through the primary secretion of glucocorticoids (GCs). Moreover, proinflammatory cytokines are produced by both tumors and chronic stress, and these can lead to neuroinflammation and change how the body reacts to stress. Another factor that could lead to a persistent proinflammatory state is anti-cancer medication [175, 180–182] (Created in BioRender: https://biorender.com/h19h122).

turn may promote tumor heterogeneity and metastasis. Notably, research conducted in the previous 2 years has revealed that glucocorticoids (GCs) and glucocorticoid receptors (GRs) are critical for the regulation of CSCs as shown in Figure 1. By lowering the expression of YAP protein, GR antagonism prevented the production of breast CSCs [180, 181]. Furthermore, GCs facilitated the maintenance of breast CSCs, cell survival, metastasis, and chemotherapy resistance by activating the interaction between GR and domain transcription factor 4 (TEAD4) [183]. Therefore, the CSCs signaling network may have its origin in the elevated glucocorticoids brought on by long-term psychological disorders. This connection underscores the importance of understanding the biological mechanisms linking stress, inflammation, and cancer progression to develop effective interventions.

3.2 | Impact on Treatment Adherence and Prognosis

One common pathophysiological process that underlies several chronic illnesses, such as cancer and stress, is persistent low-grade inflammation [175]. Persistent psychological stress leads to a noticeable and long-lasting rise in pro-inflammatory factors in the bloodstream, resulting in low-grade inflammation in the brain and peripheral tissues [184, 185]. Chronic inflammation and cancer are intricately linked, driven by common signaling pathways such as NF-kB, STAT3, and mTOR, which regulate proinflammatory cytokine production, creating a self-sustaining feedback loop [186]. The activation of NF-kB and STAT3 in concert results in the upregulation of the FAT10 gene, which in turn inhibits the function of the tumor suppressor p53 [187]. The majority of human malignancies involve the TP53 gene mutation, which usually results in the inactivation of the tumor suppressor p53. Research has demonstrated that the p53 protein mutant promotes the survival of cancer cells through increased intracellular reactive oxygen species (ROS) production, proinflammatory cytokine secretion, mTOR signaling activation, decreased autophagic activity, and increased expression of uncoupling protein 2 (UCP2) [188]. Tumor growth, metastasis, and neuroinflammation are further encouraged by proinflammatory cytokine production, which is further exacerbated by stress or hypoxia related to cancer, metabolic alterations, and anticancer therapy [189]. Microglial activation, disruption of the blood–brain barrier, and monocyte trafficking are some of the mechanisms involved in neuroinflammation [166, 190]. As an immuno-inflammatory condition, depression may play a crucial role in the relationship between inflammatory mediators and cancer, according to studies and reviews [191–197]. Depression in cancer patients can be classified as an immuno-inflammatory disorder, associated with elevated levels of proinflammatory mediators such as cytokines and acute phase proteins like CRP and haptoglobin. This association with depression is evident due to immune system activation across various cancer types, triggered by tumor cells releasing cytokines, chemokines, and growth factors, in addition to treatments and psychological stress [193, 198]. Tumor cells release cytokines like IL-6, CRP, and TNF-α, as well as chemokines, angiogenic factors, and growth factors, inducing inflammatory responses that can

promote or inhibit tumor growth. Treatments like surgery, chemotherapy, and radiotherapy associated with cancer, alongside psychological stress, can trigger the production of proinflammatory cytokines such as IL-1, INF-α, IL-6, and TNF-α [199–201]. Consequently, this stimulation could result in elevated levels of inflammatory biomarkers in patients with both cancer and depression compared to those without depression, as evidenced by IL-6 concentrations [118]. As such, depression among cancer patients is a complex phenomenon influenced by various factors including cancer type, treatment modalities, individual susceptibility, and the interplay between psychological and physiological mechanisms. Recognizing depression as an immuno-inflammatory disorder sheds light on its intricate etiology and underscores the importance of holistic approaches in managing the mental health aspects of cancer care. Further exploration of the intricate relationships between depression, cancer, and inflammation holds promise for advancing our comprehension and treatment of this prevalent comorbidity.

4 | Management Strategies for Depression in Cancer Patients

4.1 | Pharmacological Interventions

4.1.1 | Antidepressant Therapy

Antidepressant medications, such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), are commonly prescribed to alleviate depressive symptoms in cancer patients [202]. Evidence from majority reviews [202–205] suggest that antidepressants are more effective than placebo (majority evidence on SSRIs) with one review suggesting no difference between the both groups [206]. Although the overall quality of evidence is poor, some recommendations suggest the use of antidepressants in the treatment of depression, especially in severe cases [202,204]; while some withhold from making any general recommendations [203, 206]. None suggest a general contra-indication for antidepressants in cancer patients. There is emerging evidence suggesting the anti-tumor role of antidepressants [207–209].

Inflammation contributes to both cancer and psychiatric conditions, with cancer patients facing an increased risk of psychiatric disorders following diagnosis. However, the impact of nonsteroidal anti-inflammatory drugs (NSAIDs) on subsequent psychiatric disorders remain uncertain. Recent studies have found that compared to non-users, individuals using aspirin alone had a lower incidence of depression, anxiety, and stress-related disorders [210]. Further investigations also showed an association between NSAIDs and incident depression among older cancer survivors with osteoarthritis, indicating a nuanced relationship between cumulative NSAID days and incident depression [211].

4.1.2 | Adjunctive Medications for Symptom Management

In addition to antidepressants, adjunctive medications have been described in the literature to manage specific symptoms associated with depression in cancer patients. For example, benzodiazepines or buspirone for anxiety symptoms; and trazodone or mirtazapine for sleep disturbances [212].

4.2 | Role of Psychological Intervention in Cancer Patients

Several psychological interventions have demonstrated efficacy, including relaxation techniques, cognitive-behavioral therapy (CBT), mindfulness-based stress reduction (MBSR), acceptance and commitment therapy (ACT), telephonic and web-based interventions, physical exercise, yoga, and other complementary therapeutic approaches [213–217]. Studies exploring these interventions for cancer patients have demonstrated benefits in improving psychological and physical symptoms (improvements in fatigue, insomnia, depression, anxiety, pain, distress, and overall quality of life), with some also evaluating changes in biomarkers (summarized in Table 2) [249–251].

Relaxation techniques, such as deep breathing and progressive muscle relaxation, have been shown to relieve both psychological and physiological tension, thereby reducing stress and improving depressive symptoms and quality of life (QOL) in cancer patients [213, 252]. Cognitive-behavioral therapy (CBT) targets maladaptive cognitive patterns and facilitates emotional regulation, with proven efficacy in alleviating depression and enhancing QOL [217, 253]. Mindfulness-based stress reduction (MBSR), a structured intervention incorporating meditation, yoga, and related practices, has been demonstrated to effectively reduce loneliness, anxiety, and depression in cancer patients [216, 223]. Similarly, acceptance and commitment therapy (ACT) promotes psychological flexibility by encouraging patients to accept distressing thoughts without becoming overwhelmed. ACT has been found to be comparable to CBT in its ability to improve mood and QOL [254]. Furthermore, exercise therapy may offer modest benefits for depression in cancer patients. Although limited research focuses on depression as a primary outcome, meta-analytic findings suggest that exercise can reduce pain, alleviate fatigue, and improve QOL in cancer survivors [215, 255].

As such, psychological interventions tailored to the unique needs of cancer patients offer significant potential in alleviating psychological distress, improving quality of life, and influencing immune function, as demonstrated by changes in physiological (reduced heart rate and heart rate variability) [229, 230] and immunological biomarkers (changes in lymphoproliferation and cytokine production [IL6, TNF-α, IL-10] [228, 235–238], decreased serum cortisol and leptin levels, increased NK cell activity, and telomere length stabilization) [216, 219, 221, 222, 224, 231, 235].

5 | Clinical Implications

5.1 | Screening and Assessment Strategies

Implementing routine screening and assessment protocols for depression in cancer patients is essential for early detection and intervention. Validated tools such as the Patient Health Questionnaire (PHQ), Beck Depression Inventory-ii (BDI-II), and Hospital Anxiety and Depression Scale (HADS) can aid in

TABLE 2 | Effect of psychological interventions on various biomarkers.

Type of psychological intervention	Effect on biomarkers
Relaxation techniques	• Increase in T-cell proliferation [218] • Increase in mature T cells, NK cells, LAK cells, IL-1β, CD4/CD8 ratio [219] • Reduction of activity related to transcription control pathways involved in adrenergic and glucocorticoid signaling, pro-inflammatory signaling (NFkB), pro-malignant signaling (ETS1, STAT and GATA families) [220]. • Increased CD4+ T cell activity, M1 macrophage polarization and epithelial-to-mesenchymal-transition (EMT) signature [219]
Cognitive Behavioral Stress Management (CBSM) and Cognitive Behavioral Therapy (CBT)	• Increased lymphoproliferation[a] [217, 221] • Increase in IFN-γ, NK cells, IL-4, IL-10 and IL-1β production [221, 222] • Higher Th1 cytokine (IL-2 and IFN-γ) production and IL-2:IL-4 ratio [223] • Decrease in serum cortisol [224–226]
Mindfulness-based stress reduction (MBSR)	• Reduction in levels of proinflammatory cytokines (IFN-γ, TNF) with increase in anti-inflammatory cytokines (IL-4, IL-10), with a shift from Th-1 (proinflammatory) to Th-2 (anti-inflammatory) [227] • Reduced salivary cortisol and IL-6 [228] • Increase in heart rate (HR) variability[b] [229, 230] • Telomere Length (TL) was maintained (reduction in cancer patients) [216, 231]
Acceptance and Commitment Therapy (ACT)	• Reduced hsCRP and IL-1Ra levels[a] [232]
Complementary and alternative medicine therapy—Yoga intervention	• Decrease in IgA, increase in CD-56 T cells [233] • Decrease in cortisol levels [234]
Exercise therapy	• Reduced levels of IL6, TNF-α, IL-10, and leptin [235–239]
Other complementary and alternative medicine therapies (auricular point acupressure, medical Qigong therapy, body mind spirit therapy, individual massage sessions, hand-based massage, clown intervention, music therapy)	• Reduced CRP levels [240] • Reduced cortisol levels [241] • Increased NK cells [242] • Reduction in salivary Chromogranin-A [243] • Greater HR variability[b] [244, 245] • Greater telomerase activity [246] • Decrease in soluble IL-4 receptor [246]
Telephonic and web-based interventions	• Reduction in IL-10 [247] • Reduction in IL-6, IL-1β, IL-1α, IL-8 and increase in NK cells [248]

[a]Few studies found no change in inflammatory biomarkers and cortisol levels.
[b]Higher heart rate variability has been reported in healthy individuals.

identifying patients at risk of depression. Clinicians should also consider factors such as cancer type, treatment stage, and comorbidities when assessing depression risk [256].

5.2 | Tailoring Treatment Approaches

Tailoring treatment approaches to the individual needs and preferences of cancer patients is crucial for optimizing outcomes. Clinicians should consider factors such as patient preferences, treatment side effects, and psychosocial support systems when selecting interventions. A personalized approach that integrates pharmacological, psychotherapeutic, and complementary therapies may enhance treatment adherence and effectiveness [257].

5.3 | Multidisciplinary Care

Collaborative care models involving multidisciplinary teams comprising oncologists, psychiatrists, psychologists, social workers, and other healthcare professionals can facilitate comprehensive management of depression in cancer patients. CaLM Model provides coordinated, multidisciplinary treatment, which includes nutrition, genetic counselling, pharmacy, psychiatric, and financial and fertility navigation [258]. Multidisciplinary care can successfully enhance patients' quality of life by lowering their feelings of depression and anxiety and enabling them to benefit from comprehensive social support [259].

6 | Future Directions

6.1 | Emerging Research Areas

Future research should focus on elucidating the underlying mechanisms linking depression and cancer, including neurobiological, immunological, and genetic factors. Exploring novel treatment modalities, such as immune-based therapies and targeted interventions, may provide new avenues for managing depression in cancer patients. Additionally, investigating

the impact of emerging technologies, such as telemedicine and digital health interventions, on depression management holds promise for improving access to care [260].

6.2 | Challenges and Opportunities

Addressing barriers to depression care in cancer patients, including stigma, lack of awareness, limited access to mental health services, and treatment-related side effects, remains a challenge [261, 262]. Opportunities exist to integrate depression screening and management into routine oncology practice through education, training, and policy initiatives [263]. Collaborative efforts involving patients, caregivers, advocacy groups, and healthcare organizations are essential for advancing depression care in cancer settings [264, 265].

7 | Study Limitations

A comprehensive search strategy across multiple research databases was used. However, it is possible that some relevant studies were inadvertently missing, particularly those with negative or null results. This has the potential to distort review results by overstating the correlation between depression and cancer [266]. This review therefore may not have captured the full breadth and variability of the content included within these interventions, especially those targeting the treatment methods and holistic care plans. The biological interplay between cancer and depression is still needed to be fully understood. Factors such as inflammation, neuroendocrine dysregulation, and genetic predisposition may play roles, but research in this area is still evolving.

8 | Conclusion

Depression is a prevalent and complex comorbidity in cancer patients, with significant implications for clinical practice and patients. Depression in cancer patients is influenced by a complex interplay of neurobiological, immunological, genetic, and epigenetic factors. Dysregulation of neurotransmitter systems, dysfunction of the HPA axis, inflammatory responses, immune system modulation, genetic susceptibility, and epigenetic modifications contribute to the pathophysiology of depression in this population. Chronic stress can lead to the sustained release of proinflammatory cytokines, maintaining cells in an inflammatory state that influences immune responses and inflammation associated with cancer progression. The observed genetic correlation and potential relationship between stress-induced depression and cancer highlight the complex interplay between chronic stress, inflammation, immune responses, and cancer development. As discussed above, from relaxation techniques and CBT to exercise therapy and digital interventions, a diverse array of approaches has shown promise in addressing the multifaceted challenges faced by cancer patients. By incorporating these interventions into comprehensive cancer care, healthcare providers can better support patients in navigating the emotional and psychological aspects of their illness, ultimately enhancing their overall well-being and treatment outcomes. As such, the management of depression in cancer patients involves a multidisciplinary approach encompassing pharmacological interventions, psychotherapeutic approaches, and integrative therapies. Antidepressant therapy, CBT, mindfulness-based interventions, and exercise programs are among the strategies used to alleviate depressive symptoms and improve psychological well-being in this vulnerable population.

Further research into the psychobiological underpinnings of depression in cancer patients is warranted to inform the development of targeted interventions aimed at improving mental health outcomes in this vulnerable population. Screening, assessment, and tailored treatment approaches are essential for addressing depression in this population [267]. Multidisciplinary care models that integrate oncology and mental health services can improve depression management and quality of life for cancer patients as summarized in Figure 2 [28, 258]. Researchers should prioritize understanding the mechanisms underlying depression in cancer patients and exploring innovative approaches to prevention and treatment [99]. Clinicians should advocate for

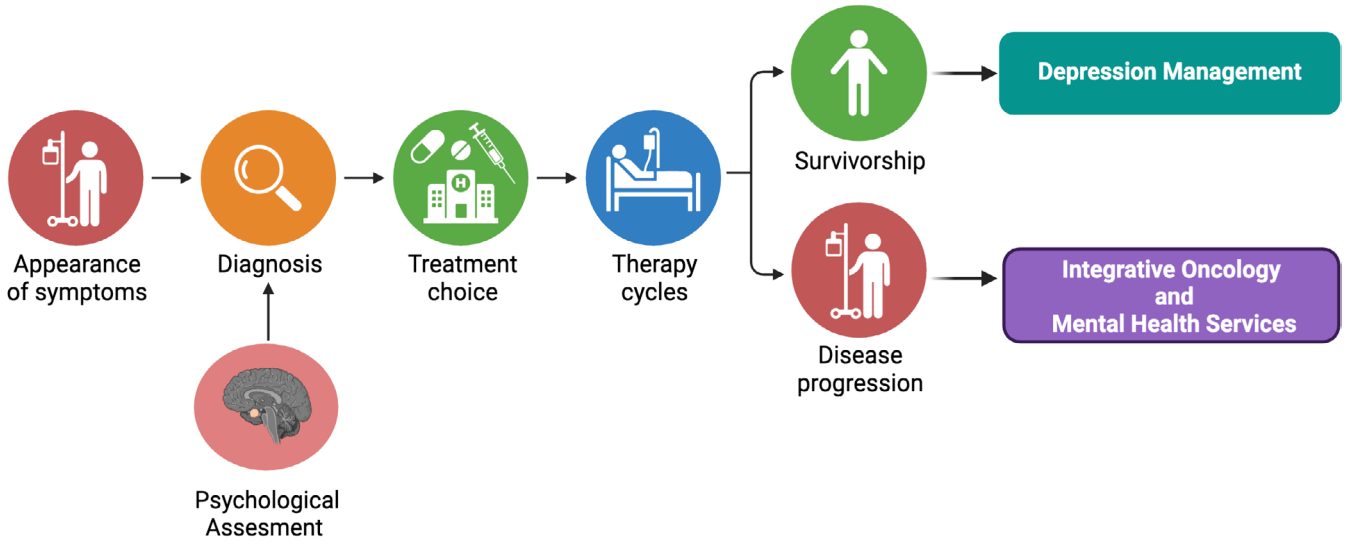

FIGURE 2 | The essential components required to construct a program for coping with cancer are emphasized (The image has been inspired by Cortiana et al. [28]) (Created in BioRender: https:/biorender.com/h19h122).

the integration of mental health services into cancer care settings and collaborate with interdisciplinary teams to enhance depression screening and management [259]. By addressing the psychosocial needs of cancer patients, healthcare providers can optimize outcomes and improve the overall patient experience.

Author Contributions

The authors declare that they have made substantial contributions to this manuscript. Joyeeta Talukdar, Megha, Hemant Choudhary and Pratap Sharan were involved in the conceptualization, analysis, and interpretation of data and critical revision of this manuscript. Pratap Sharan, Sushma Bhatnagar, Subhradip Karmakar, Anuja Pandit and Ashwani Kumar Mishra gave final approval for publication and agreed to be responsible for all aspects of the work.

Acknowledgments

The authors thank Department of Health Research for supporting our research vide grant no DHR-1534 (File Number: R.11012/04/2023-GIA/HR).

Ethics Statement

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

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