Psycho-Oncologie 2025, 19(1), 3596.
https://doi.org/10.18282/po3596

Article

Impact of stress on tumor progression and the molecular mechanisms of exercise intervention: From psychological stress to tumor immune escape

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CITATION

Du X, Jiang F, Fan R, Kong J. Impact of stress on tumor progression and the molecular mechanisms of exercise intervention: From psychological stress to tumor immune escape. Psycho-Oncologie. 2025; 19(1): 3596. https://doi.org/10.18282/po3596

ARTICLE INFO

Received: 14 November 2024
Accepted: 31 December 2024
Available online: 3 January 2025

Abstract: Psychological stress is prevalent among cancer patients and has significant effects on both tumor progression and the mental health of patients. Through a biopsychosocial pathway, psychological stress impacts immune function, facilitates inflammatory responses, and hasten tumor growth and metastasis. Consequently, investigating effective ways to mitigate the negative impact of stress on cancer progression holds significant clinical relevance. This review seeks to summarize existing research to delve into the molecular mechanisms by which psychological stress hasten tumor progression and to discuss the potential mechanisms by which exercise, as a non-pharmacological intervention, may mitigate tumor development and enhance the mental health of cancer patients by regulating stress responses. Through a comprehensive analysis of relevant literature, we explore the impact of psychological stress on tumor biology, notably through the activation of the hypothalamic-pituitary-adrenal (HPA) axis, the sympathetic nervous system (SNS), and the promotion of immunosuppression and inflammation. Besides, we review articles on how exercise intervenes in tumor progression by regulating the HPA axis, SNS, strengthening immune function, and suppressing angiogenesis and metastasis. Research confirmed that psychological stress hasten tumor proliferation and metastasis through multiple pathways (e.g., activation of the HPA axis and SNS, pro-inflammatory responses). Exercise may decelerate tumor progression by regulating stress hormone levels, strengthening the immune system function, and lowering the activity of pro-cancer signaling pathways such as VEGF. In addition, exercise boosts the mental health of cancer patients, lowering the incidence of anxiety and depression and enhancing treatment adherence.

Keywords: stress; tumor progression; exercise intervention; molecular mechanisms; psychological stress; tumor immune escape

1. Introduction

In the course of the treatment of cancer patients, psychological stress has been extensively identified as a critical factor impacting both the physical and mental health of patients, as well as the outcomes of treatment. Researches have confirmed that psychological stress may not only cause emotional issues like anxiety and depression but also affect cancer progression through various physiological mechanisms. For instance, stress may hasten tumor growth and metastasis by modifying immune and endocrine functions [1,2]. Specifically, anxiety and depression are extremely prevalent among cancer patients, with approximately 20% facing depression and 10% suffering from anxiety [3]. These psychological problems not only affect the quality of life of patients but may also decrease treatment adherence, ultimately affecting cancer survival rates. Hence, the effective management of psychological stress in cancer

patients, intended to optimizing both their physical and mental well-being, has become a focus of clinical and research interest.

The biopsychosocial model of stress reveals that psychological stress impacts physical health through multiple pathways. First, psychological stress activates the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS), both of which produce direct physiological effects by secreting hormones such as cortisol and adrenaline. The release of these hormones can impact the immune system, weakening the body's anti-tumor immune response and enhancing susceptibility to disease [2–4]. In addition, prolonged psychological stress has been tightly associated with increased inflammation and enhanced angiogenesis. This sustained stress not only facilitates the growth of tumor cells but may also increase the risk of metastasis [5]. Consequently, psychological stress is not merely a mental health issue; it has significant effects on tumor progression and dissemination through complex physiological mechanisms.

Lately, numerous studies have confirmed that exercise can effectively mitigate psychological stress in cancer patients and enhance their physiological function. The regulatory effects of exercise on the HPA axis and SNS, notably by lowering the secretion of stress hormones, are crucial for stress management in cancer patients. Research has demonstrated that exercise can decrease levels of inflammatory markers, such as interleukin-6 (IL-6), while strengthening the function of anti-tumor immune cells like T cells and natural killer (NK) cells, thereby suppressing tumor progression [6,7]. Furthermore, the positive effects of exercise on mental health are well established. Moderate exercise can significantly reduce anxiety and depression levels in cancer patients and enhance their quality of life [8]. investigating the role of exercise intervention in the stress management of cancer patients, especially its potential molecular mechanisms, has become an important direction in clinical applications.

This review seeks to combine current mechanistic research on how psychological stress hastens tumor progression through physiological pathways and to delve into the role of exercise interventions in easing psychological stress, strengthening anti-tumor capabilities, and optimizing the quality of life forcancer patients. By investigating these mechanisms and effects, this review may offer a theoretical basis for future personalized treatment plans for cancer patients, encouraging the broader application of exercise interventions in cancer rehabilitation.

2. Psychological stress in cancer patients

In the treatment process of cancer patients, psychological stress is an important factor that impacts their quality of life and treatment outcomes. To better understand the sources of this psychological stress and its impact on patients' physical and mental health, psychological stress in cancer patients can be analyzed in depth from several aspects. **Figure 1** depicts the sources, effects and management of psychological stress in cancer patients.

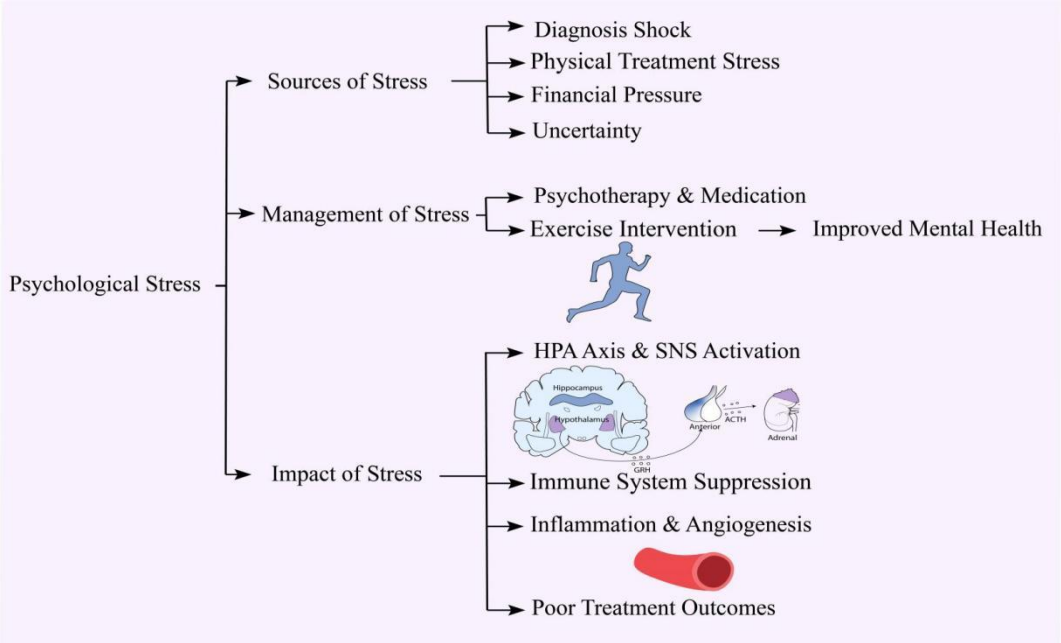

Figure 1. The sources, effects and management of psychological stress in cancer patients.

2.1. Sources of psychological stress

The psychological stress experienced by cancer patients originates from several key sources, which have been extensively studied and discussed. The diagnosis of cancer often results in a significant mental shock, leading to anxiety and fear, notably when patients face life-threatening situations and uncertainties regarding treatment outcomes [9]. The physical stress associated with treatment, including side effects from chemotherapy and radiotherapy such as fatigue, pain, and nausea, significantly worsens the psychological burden on patients [9]. In addition, the high cost of cancer treatment imposes serious financial pressure on patients and their families, contributing to psychological distress [9]. Lastly, the uncertainty regarding prognosis causes patients to worry about recurrence, metastasis, and survival rates, creating sustained psychological stress that significantly impacts their mental and physical health [9].

2.2. Impact of psychological stress on cancer patients

Psychological stress not only worsens the mental burden on cancer patients but also hastens disease progression through various physiological mechanisms. Researches have confirmed that stress activates the HPA axis and the SNS, enhancing the secretion of stress hormones such as cortisol and adrenaline. High levels of these hormones suppress immune system function, notably by suppressing the activity of T cells and SNS cells, which decreases the body's ability to fight tumors [2–10]. In addition, long-term psychological stress fosters inflammation and angiogenesis, providing favorable conditions for tumor cell proliferation and metastasis. Chronic stress induces an inflammatory response that alters the tumor microenvironment, further encouraging cancer development [10,11]. These mechanisms explain the close association between prolonged stress and tumor progression coupled with prognosis.

Researches confirmed that anxiety and depression in cancer patients are strongly

associated with poorer treatment outcomes and lower survival rates. Emotional distress can severely impact treatment adherence, impacting patients' ability to take medications on time and communicate effectively with healthcare providers [12]. Studies have also pointed out that anxiety and depression not only diminish patients' quality of life but also impair their ability to cope with illness, negatively affecting overall treatment outcomes [12]. Managing mental health is notably important in cancer treatment, as optimizing psychological well-being can significantly enhance both the quality of life and treatment adherence [12].

2.3. Management of psychological stress

Effectively managing the psychological stress of cancer patients is crucial for optimizing their quality of life and treatment outcomes. Traditional stress management methods include psychotherapy, medication, and social support. In recent years, studies have confirmed that exercise interventions can effectively enhance the mental health of cancer patients and, by strengthening immune function and lowering tumor progression, demonstrate great potential [13]. Research also suggests that exercise regulates stress-related endocrine systems, such as the release of hormones, which positively impact on the cancer immune microenvironment [13].

Exercise not only decreases levels of pro-inflammatory cytokines like IL-6 but also boosts the activity of T cells and NK cells, which play vital roles in the body's anti-tumor response. Consequently, exercise can help to prevent cancer progression, lower the risk of recurrence, and enhance overall survival rates. Furthermore, the mental health benefits of exercise, including reductions in anxiety and depression, are well-documented, further emphasizing its role in comprehensive cancer care [13]. Thus, integrating exercise interventions into cancer treatment plans not only supports physical recovery but also offers crucial psychological and emotional benefits, underscoring its value as a holistic approach in cancer care.

3. Effects of stress on tumor progression: Physiological and molecular mechanisms

3.1. Activation of the HPA axis and SNS

In the stress response, the body responds through several interrelated physiological systems, the most critical of which are the HPA axis and the SNS. These two systems work together to release stress hormones that regulate the body's internal balance. However, when the stress response is prolonged, over-activation of the HPA axis and SNS causes a series of complex pathological changes, especially prominent in interactions with diseases such as cancer. **Figure 2** depicts the mechanism of activation of the HPA axis and SNS under chronic stress conditions and its role in tumor biology.

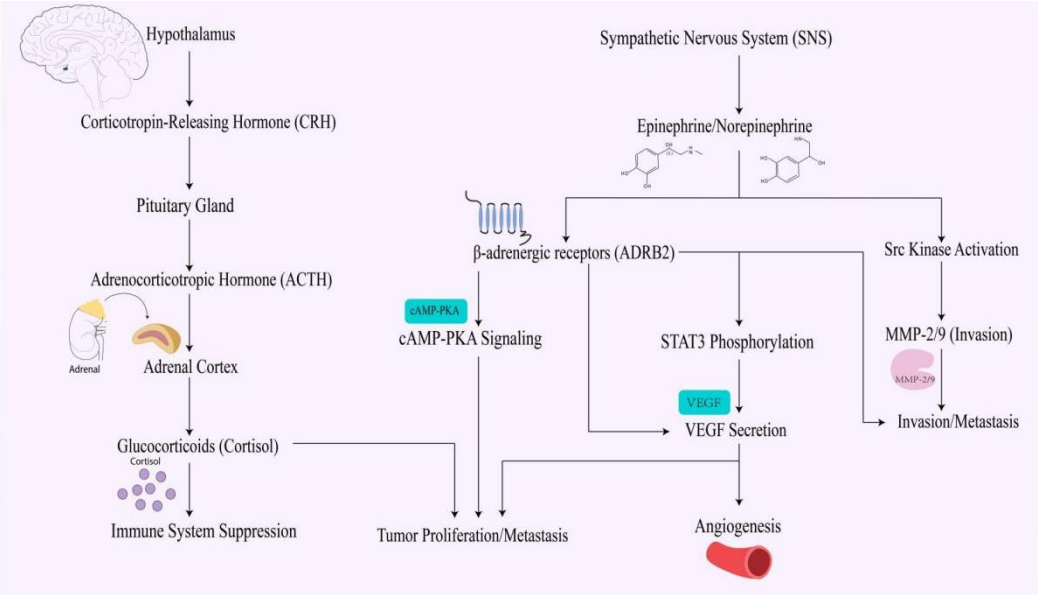

Figure 2. Mechanism of activation of the HPA axis and SNS under chronic stress conditions and its role in tumor biology.

3.1.1. HPA axis stress response

In chronic stress conditions, the overactivation of the HPA axis is a central feature of numerous pathological processes. Stress stimuli lead the hypothalamus to release corticotropin-releasing hormone (CRH), which stimulates the pituitary gland to secrete adrenocorticotropic hormone (ACTH), ultimately resulting in the adrenal cortex releasing significant amounts of glucocorticoids, such as cortisol [14]. Elevated cortisol levels suppress the immune system and regulate various signaling pathways within the tumor microenvironment, affecting tumor proliferation, angiogenesis, and metastasis. For example, prolonged high cortisol levels weaken anti-tumor immune responses, enabling tumor cells to evade immune surveillance, and thereby accelerating tumor growth [14,15]. In addition, sustained chronic inflammation may hasten tumor progression [15]. This complex stress-immune regulatory network demonstrates that stress not only impacts immune cells but also facilitates cancer progression via neuroendocrine pathways.

3.1.2. Impact of the sympathetic nervous system

Stress has significant tumor-encouraging effects through the activation of the SNS. Under stress, SNS activation causes the release of large amounts of epinephrine and norepinephrine. These stress hormones act on β-adrenergic receptors within cancer cells and the tumor microenvironment, affecting multiple signaling pathways. Research confirmed that epinephrine facilitates cancer cell proliferation and metastasis by activating the cAMP-PKA signaling pathway [10–16]. Besides, sustained SNS activation boosts angiogenesis and facilitates cancer cell invasion and metastasis through mechanisms such as matrix degradation. These changes worsen cancer progression and negatively affect patients' psychological health [17,18]. Consequently, excessive SNS activation is considered a key factor in tumor progression.

3.1.3. Effects of stress on tumor biology

Stress hormones exert significant influence on the biological properties of tumor

cells by activating β-adrenergic receptors (ADRB2). Studies confirm that ADRB2 activation can stimulate cancer cell proliferation and inhibit apoptosis. For example, stress hormones such as norepinephrine and epinephrine activate downstream signaling pathways via ADRB2, enhancing intracellular levels of cyclic adenosine monophosphate (cAMP) levels and activating molecules such as protein kinase A (PKA), which inhibit apoptosis-related proteins and enhance cancer cell survival [19,20]. In addition, ADRB2 activation facilitates tumor angiogenesis by upregulating the expression of vascular endothelial growth factor (VEGF), thereby providing an increased blood supply for tumor growth. Stress hormones binding to ADRB2 also stimulate VEGF secretion, which can occur via mechanisms such as the phosphorylation of signal transducer and activator of transcription 3 (STAT3), thereby strengthening tumor neovascularization [20,21]. Besides, stress hormones increase cancer cell invasiveness and metastatic potential. Studies confirm that norepinephrine mediates the activation of Src kinase via ADRB2, strengthening cancer cell migration and invasion, a process associated with the upregulation of matrix metalloproteinases (MMP-2, MMP-9), which further facilitates tumor invasion and metastasis [20,21]. These findings highlight the significant role that stress hormones play through ADRB2 signaling in encouraging tumor proliferation, anti-apoptosis, angiogenesis, and metastasis.

3.2. Immune evasion and exacerbation of inflammatory responses

Chronic stress not only weakens the anti-tumor capacity of the immune system through multiple pathways, but also facilitates worsening inflammation through complex signaling pathways. **Figure 3** exemplifies the mechanism of immune escape and exacerbation of inflammatory response due to chronic stress.

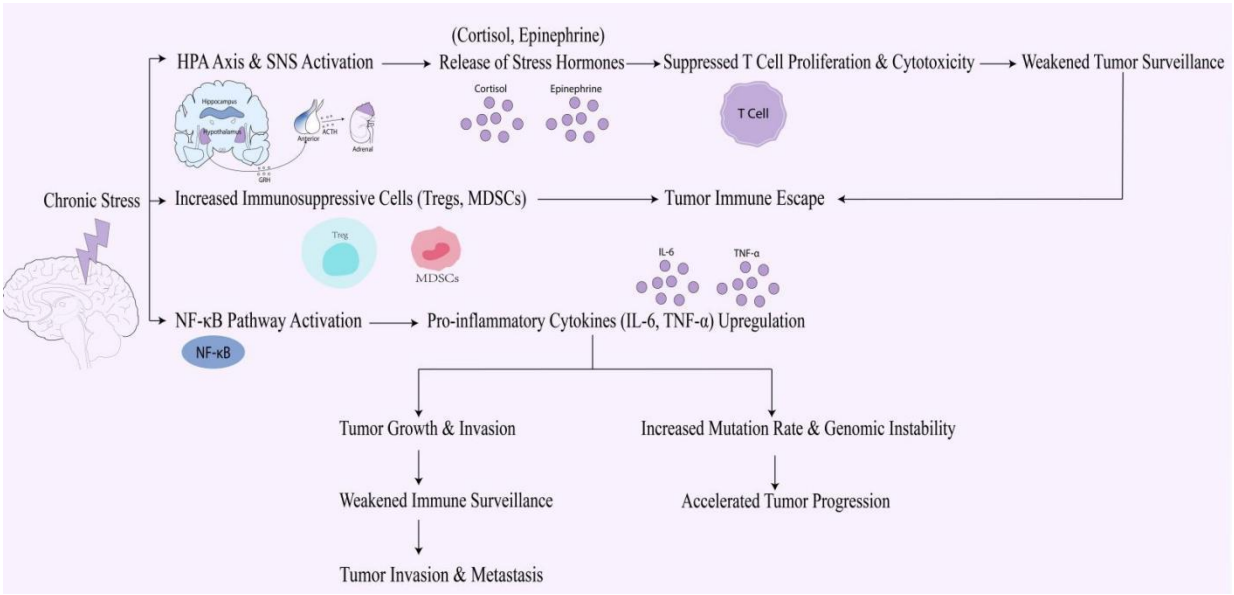

Figure 3. Mechanism of immune escape and exacerbation of inflammatory response due to chronic stress.

3.2.1. Immunosuppressive effects

Stress-induced immunosuppression plays a critical role in tumor progression. In chronic stress conditions, the function of anti-tumor immune cells, such as T cells and

NK cells, is significantly impaired. Studies confirm that chronic stress activates the HPA axis and SNS, leading to the release of stress hormones like cortisol and epinephrine, which suppress T cell proliferation and cytotoxicity, weakening immune surveillance against tumors [15–22]. Besides, chronic stress facilitates the increase of immunosuppressive cells, notably regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), which secrete immunosuppressive factors that further disrupt anti-tumor immune responses and facilitate tumor immune escape [23]. These mechanisms indicate that chronic stress not only weakens the immune system's ability to fight tumors but also facilitates tumor growth and metastasis [22]. Consequently, managing chronic stress or intervening in related neuroendocrine pathways may emerge as new strategies to enhance cancer treatment outcomes.

3.2.2. Exacerbation of pro-inflammatory states

Chronic stress is tightly associated with inflammation, and studies have confirmed that it can worsen inflammatory responses through the activation of multiple pro-inflammatory pathways, notably the NF-κB pathway. Stress hormones, such as norepinephrine and cortisol, can induce the activation of these pathways, leading to the upregulation of pro-inflammatory cytokines such as IL-6 and tumor necrosis factor-α (TNF-α). These cytokines stimulate tumor growth and invasion within the tumor microenvironment by affecting fibroblasts, endothelial cells, and immune cells [11–15]. In addition, persistently high levels of inflammatory cytokines increase the mutation rate and genomic instability in cancer cells, accelerating tumor progression [10]. This inflammatory response not only directly facilitates cancer cell proliferation and survival but also weakens the immune system's tumor surveillance capabilities, further driving tumor invasion and metastasis [10–15].

3.3. Promotion of angiogenesis and metastasis

The role of stress hormones is in tumor angiogenesis and metastasis. They have significant effects on the tumor microenvironment through multiple signaling pathways, especially in encouraging angiogenesis and tumor invasion. **Figure 4** illustrates Stress Hormone-Induced Promotion of Angiogenesis, Tumor Growth, and Metastasis.

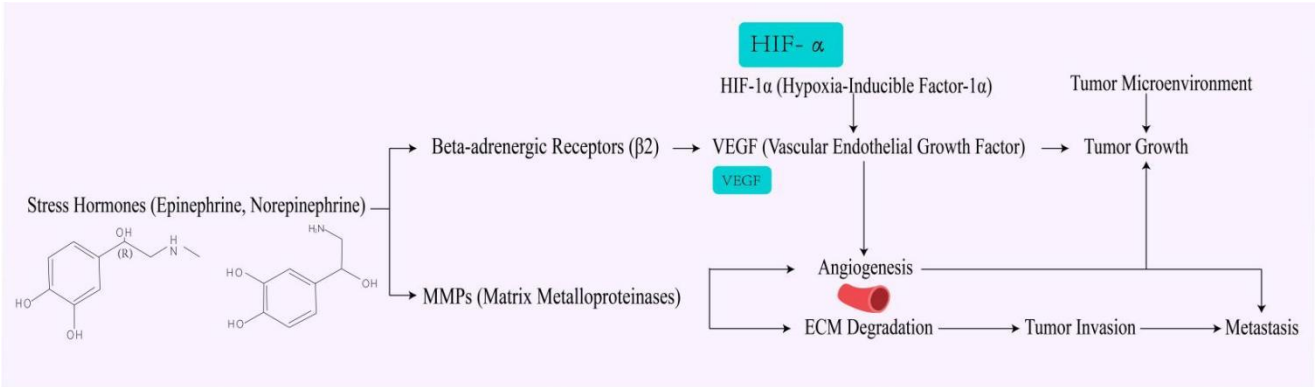

Figure 4. Stress hormone-induced promotion of angiogenesis, tumor growth, and metastasis.

3.3.1. Upregulation of the VEGF signaling pathway

Stress hormones stimulate tumors angiogenesis by strengthening the expression

of VEGF, a key mechanism for tumors growth and spread. Stress hormones like epinephrine and norepinephrine upregulate VEGF expression by activating β-adrenergic receptor signaling, notably the β2 receptor. This pathway not only stimulates blood vessel formation but also increases tumors invasiveness and metastatic potential through downstream molecules like matrix metalloproteinases (MMPs)[10–24]. In addition, under hypoxic conditions, VEGF expression is regulated by hypoxia-inducible factor-1α (HIF-1α), enabling tumors to sustain rapid growth even in harsh microenvironments [17–23]. Angiogenesis not only offers nutrients and oxygen for tumors growth but also creates pathways for cancer cells to metastasize to distant organs, significantly enhancing the aggressiveness and spread of the tumors [24]. These mechanisms demonstrate the critical role of stress hormones and VEGF in shaping the tumors microenvironment and driving tumor growth and progression.

3.3.2. Activation of MMPs

The activation of MMPs by stress significantly contributes to tumor invasion and metastasis. MMPs are enzymes involved in the degradation of the extracellular matrix (ECM), and the expression of MMP-2 and MMP-9 is markedly upregulated under stress conditions. These enzymes break down tissue barriers, making it easier for cancer cells to detach from the primary tumor and migrate to other locations. The release of stress hormones boosts the expressions and activity of MMPs, accelerating ECM degradation and creating pathways for cancer cell metastasis [25]. Research confirmed that MMP-2 and MMP-9 play pivotal roles not only in tumor invasion but also in angiogenesis, linking them tightly with tumor growth, vascular development, and metastasis in aggressive cancers such as gastric cancer and melanoma [25,26]. In addition, MMP overexpression often occurs at the tumor-stroma interface, indicating their crucial role in multiple stages of cancer development [25].

4. The role of exercise intervention in lowering stress and optimizing tumor progression: Molecular mechanisms

Exercise, as a non-pharmacological intervention, has been extensively studied and proven to decrease psychological stress and enhance tumor progression through various molecular mechanisms. Exercise not only regulates physiological systems, such as the HPA axis and the SNS, but also decelerates tumor deterioration by strengthening immune function, reducing inflammation, and suppressing angiogenesis and metastasis. Furthermore, exercise has a significant positive impact on the mental health of patients, helping them better cope with psychological stress. The following sections offer a detailed discussion of the multi-layered benefits of exercise interventions in reducing stress and optimizing tumor progression. **Figure 5** depicts the molecular mechanisms of exercise interventions in lowering stress and optimizing tumor progression.

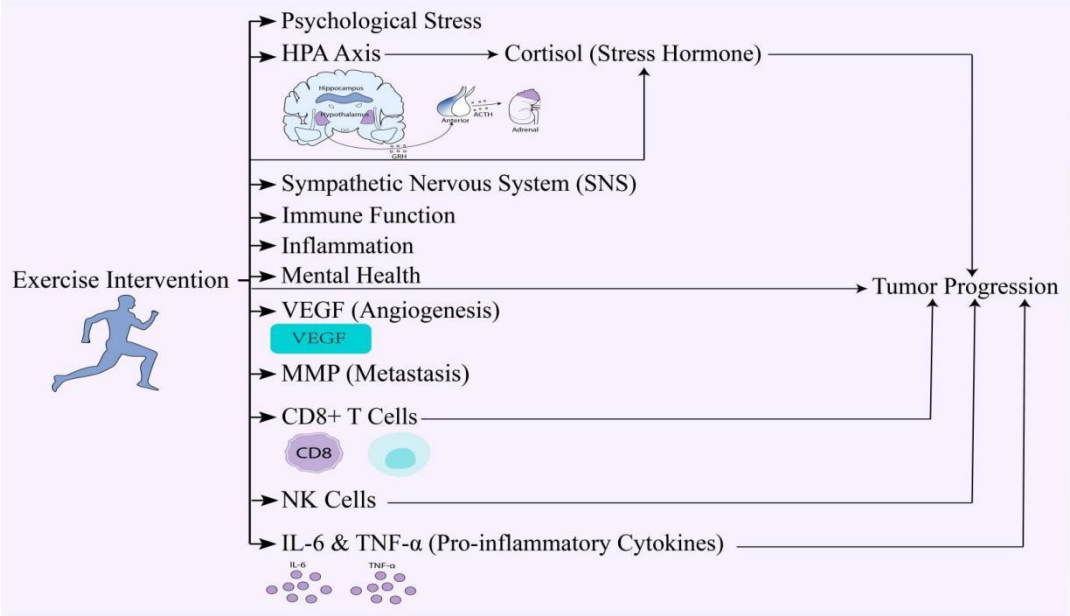

Figure 5. Molecular mechanisms of exercise interventions in lowering stress and optimizing tumor progression.

Exercise intervention regulates the HPA axis and the SNS, reducing the secretion of stress hormones such as cortisol and adrenaline. It enhances immune function by increasing the activity of CD8+ T cells and NK cells, suppresses pro-inflammatory cytokines like IL-6 and TNF-α, and decreases the expression of VEGF and MMPs, thereby inhibiting tumor angiogenesis and metastasis. Additionally, exercise improves mental health by alleviating anxiety and depression, creating a synergistic effect that mitigates the negative impact of stress on tumor progression through multiple molecular pathways.

4.1. Regulation of the HPA axis and SNS through exercise

4.1.1. Negative feedback regulation of the HPA axis

Chronic psychological stress causes the overactivation of the HPA axis, resulting in the prolonged elevation of stress hormones like cortisol, which is associated with various health issues such as immunosuppression and hastened cancer progression. Studies have confirmed that HPA axis overactivation impacts the hippocampus in the brain, weakening its ability to regulate HPA axis activity through negative feedback and leading to systemic immune dysfunction [27]. Exercise has been proven to be an effective method for regulating excessive HPA axis activity, especially aerobic exercise. By strengthening the body's negative feedback mechanisms, exercise helps lower plasma cortisol levels and mitigates the adverse effects of stress on the immune system [27]. Moderate aerobic exercise helps decrease the suppression of immune surveillance caused by chronic stress, thereby optimizing patients' immune function [11]. In addition, the regulation of the HPA axis through exercise decreases the risk of cancer progression associated with high cortisol levels [11].

Studies have confirmed that regular exercise significantly boosts an individual's ability to cope with stress, notably by lowering the overactivation of the HPA axis. Regular exercise boosts the body's stress response, helping to control the release of stress-related hormones like cortisol, thereby mitigating the negative effects of stress

on the body [28,29]. This negative feedback regulation not only boosts the physiological health of cancer patients but also mitigates their anxiety and depression, creating a positive psychophysiological interaction [29].

4.1.2. Decreased SNS activity

Excessive activation of the SNS in the course of stress causes the release of epinephrine and norepinephrine, which significantly enhance pro-cancer signaling pathways in the tumor microenvironment, encouraging tumor growth and metastasis. These stress hormones activate the β-adrenergic receptors on cancer cells, causing various pro-cancer responses, including increased cancer cell proliferation, enhanced anti-apoptotic mechanisms, and the promotion of epithelial-mesenchymal transition (EMT), which increases the migration and invasion capabilities of tumor cells [30,31]. Studies have confirmed that moderate exercise can decrease SNS activity, decrease the secretion of epinephrine and norepinephrine, and decrease their adverse effects on the tumor microenvironment. Exercise helps decrease the sustained activation of β-adrenergic receptors, suppressing cancer cell proliferation and metastasis. Furthermore, exercise boosts immune system function by strengthening the activity of anti-tumor immune cells, such as CD8+ T cells, which further suppress tumor growth and progression [30–32].

In addition, exercise boosts the overall balance of the autonomic nervous system, notably by strengthening parasympathetic activity and lowering excessive SNS activation, effectively regulating the body's stress response. This adjustment helps decrease pro-cancer factors in the tumor microenvironment, such as VEGF and pro-inflammatory cytokines, thereby suppressing tumor development [33]. Research confirmed that sustained physical exercise not only decreases SNS activity but also facilitates overall body balance by strengthening parasympathetic function [34].

4.2. Enhancement of immune function through exercise

4.2.1. Activation of T cells and NK cells

Exercise significantly boosts immune surveillance, notably by encouraging the activation of T cells and SNS cells. Studies confirm that regular exercise increases both the number and functionality of these cells, optimizing their efficiency in recognizing and eliminating cancer cells [7–35]. Exercise not only mobilizes a large number of immune cells into the bloodstream but also boosts their migration and infiltration into tumors, restoring the body's immune surveillance capabilities [7]. Psychological stress has been confirmed to suppress T cell and NK cell activity, but exercise effectively reverses this suppression, strengthening the body's anti-tumor immune response [7].

Moderate aerobic exercise significantly increases the number and cytotoxic activity of CD8+ T cells and NK cells in peripheral blood. This phenomenon has been validated in multiple studies, which have confirmed that after acute exercise, the proportion of CD8+ T cells and NK cells in the bloodstream increases significantly, and this increase may be associated with their migration to tumor tissues [36]. In animal experiments, aerobic exercise has been found to induce more CD8+ T cell infiltration into tumors, inhibit tumor growth, and prolong survival. The increase in these cells directly contributes to the suppression of tumor cell growth and decreased

tumor metastasis [37]. Besides, the mobilization and enhanced cytotoxicity of immune cells induced by exercise can improve patient responses to chemotherapy or immunotherapy, partly due to exercise-induced metabolic and immune microenvironment changes [36,37].

4.2.2. Reduction of pro-inflammatory states

Exercise decreases tumor growth and spread by suppressing the secretion of pro-inflammatory cytokines, such as IL-6 and TNF-α, thereby lowering the activation of pro-inflammatory pathways like NF-κB. Studies have confirmed that these pro-inflammatory factors in chronic inflammation significantly drive tumor progression by activating the NF-κB pathway [38,39]. In the course of stress, the levels of these factors increase in the tumor microenvironment, but regular exercise can decrease their expression, slowing tumor progression. In addition, exercise raises levels of anti-inflammatory cytokines, such as IL-10, which helps restore immune balance in the tumor microenvironment and decelerate cancer cell proliferation and invasion [38]. These findings highlight the important role of exercise in regulating the tumor microenvironment.

4.3. Inhibition of angiogenesis and metastasis by exercise

4.3.1. Inhibition of VEGF signaling pathway

Under stress, the expression of VEGF increases significantly, encouraging tumor angiogenesis, supplying blood to cancer cells, and facilitating their growth and metastasis. However, exercise interventions have been found to inhibit this process through various mechanisms. Studies confirm that exercise not only decreases stress-induced VEGF expression but also impacts tumor progression by regulating inflammation-related factors in the tumor microenvironment [6–40]. Additionally, exercise inhibits the binding of VEGF to its receptor VEGFR, thereby suppressing angiogenesis through the regulation of multiple angiogenesis-related pathways, such as HIF-1α and eNOS [41]. These biological effects induced by exercise help decrease blood supply to tumor tissue, lower malignancy, and reduce the occurrence of distant metastasis [42]. Consequently, appropriate exercise not only directly disrupts tumor nutrition but also further suppresses tumor growth and metastasis by optimizing immune function [6].

4.3.2. Reduction of MMP activity

MMPs degrade the ECM and basement membrane, facilitating cancer cell migration into surrounding tissues and enhancing the likelihood of distant metastasis. Under stress conditions, MMP activity increases, a process observed in various cancer types [26–43]. Studies confirm that exercise regulates the activity of MMP-2 and MMP-9. Regular exercise significantly lowers the expression of these enzymes, lowering matrix degradation and cancer cell invasiveness. For example, the overexpression of MMP-9 is often associated with high invasiveness and metastatic potential in tumors, while exercise decreases MMP-9 activity, suppressing cancer cell angiogenesis and distant metastasis [26–43]. In addition, exercise can enhance the prognosis of cancer patients by regulating MMP activity, lowering the risk of cancer recurrence and spread [44].

4.4. Positive effects of exercise on mental health

4.4.1. Regulation of endorphins and neurotransmitters

Exercise is widely identified for its ability to significantly mitigate anxiety and depression in cancer patients by regulating neurotransmitter and endorphin levels. Studies confirm that exercise increases endorphin, serotonin, and dopamine levels, chemicals closely associated with improved mood and well-being. The increase in endorphins offers a "feel-good" sensation that effectively decreases anxiety symptoms, while the rise in dopamine and serotonin helps alleviate depression and enhances the overall mental health of cancer patients [45,46]. Furthermore, exercise helps patients cope with the psychological stress of cancer by regulating the brain's reward system, optimizing mood regulation, and enhancing life satisfaction [46]. Thus, exercise, as a non-pharmacological intervention, has significant positive effects on the mental health of cancer patients.

4.4.2. Enhanced coping ability

Exercise, as a non-pharmacological psychological intervention, helps enhance cancer patients' coping abilities and mitigate cancer-related fatigue (CRF). Research confirmed that exercise helps patients decrease stress responses, increase their sense of control over the disease, and enhance self-efficacy. These psychological enhancements enable patients to better cope with the challenges of treatment, thereby strengthening treatment adherence and quality of life [47,48]. Furthermore, regular exercise interventions offer patients with social opportunities and emotional support, which help mitigate feelings of loneliness and helplessness. Through exercise, patients can build greater psychological resilience, better cope with the side effects of cancer and its treatments, and enhance both psychological and physical health outcomes [47].

4.4.3. Immunity and exercise intensity

Mild exercise, such as walking or stretching, exerts a moderate immunomodulatory effect that helps maintain immune homeostasis, but its ability to enhance antitumor immunity may be limited. For instance, although exercise can promote the mobilization of NK cells and CD8+ T cells, its enhancing effect is primarily short-term following acute exercise, with minimal long-term impact [36].

Moderate-intensity exercise, such as brisk walking or cycling, has been identified as the optimal level for enhancing immune function. Research shows that it boosts immune surveillance by increasing the recruitment and activity of CD8+ T cells and NK cells, while also reducing systemic inflammation and stress-related hormones such as cortisol [49].

Intense exercise, particularly high-intensity interval training (HIIT), temporarily elevates cortisol levels, potentially leading to a transient suppression of immune function [50]. However, long-term regular high-intensity exercise can improve immune function by enhancing recovery mechanisms, though overtraining without adequate recovery may result in immune suppression [50].

4.4.4. Psychological stress and exercise intensity

Mild exercise is particularly effective in alleviating mild anxiety and promoting relaxation, which is beneficial for patients suffering from severe fatigue or physical decline. Moderate-intensity exercise is widely recognized for its ability to reduce

psychological stress, alleviate symptoms of anxiety and depression, and improve overall mental health. Studies show that moderate aerobic exercise, such as running, swimming, and cycling, has significant benefits for mental health, especially in reducing symptoms of anxiety and depression [51]. This intensity of exercise appears to balance physiological activation and recovery, thus providing optimal psychological benefits.

4.5. The role of different types of exercise in coping with psychological stress

In modern society, psychological stress has become a prevalent issue. Research indicates that different types of exercise have significant effects in alleviating psychological stress. Aerobic exercise is widely considered an effective way to improve mental health. Studies show that aerobic exercises, such as Tai Chi, not only improve physical health but also effectively reduce anxiety and depressive symptoms [52]. One study found that after 8 weeks of aerobic training, participants showed significant improvements in mental state, and their cardiovascular recovery capacity was enhanced [53].

Additionally, Tai Chi, a traditional mind-body exercise, has received increasing attention in recent years. Tai Chi practice has been found to effectively lower stress levels and improve mental health. Research shows that participants in Tai Chi groups exhibited significantly greater improvements in anxiety and stress perception compared to the waitlist group [52]. Moreover, Tai Chi is considered a low-intensity exercise suitable for people of all ages, particularly the elderly [54].

Yoga is another effective form of exercise for coping with psychological stress. Studies have shown that yoga practice significantly enhances participants' self-esteem and quality of life, while reducing depressive symptoms [55]. In a comparison between yoga and resistance training, the yoga group showed greater improvements in fatigue, self-esteem, and quality of life [56].

In conclusion, various types of exercise have shown positive effects in managing psychological stress. Aerobic exercise, Tai Chi, yoga, and hiking each have their unique characteristics and can provide effective mental health support for different populations.

4.6. Gender differences in exercise interventions

In terms of exercise interventions, although the basic principles are similar between men and women, there may be differences in the choice of exercise type, intensity, and frequency. For example, research indicates that women rely less on carbohydrates during moderate-intensity endurance exercise compared to men, which may affect their performance and adaptation during exercise interventions [57]. Additionally, women show different physiological responses after high-intensity exercise compared to men, particularly in the changes of brain-derived neurotrophic factor (BDNF) levels in the blood, where women's responses may not be as pronounced as those in men [58]. These gender differences need to be considered in the design of exercise interventions to better meet the needs of both sexes.

Furthermore, for different types of exercise interventions, studies have found that

multi-component exercise programs (such as combining strength and aerobic exercises) have a more significant effect on improving cognitive function in elderly women [59]. In elderly men, combining resistance training and aquatic exercise has also shown positive effects on combating oxidative stress [52]. These findings suggest that the effectiveness of exercise interventions may vary by gender, so considering gender differences when designing personalized exercise plans is crucial.

The frequency and duration of exercise interventions may also influence health-related outcomes. Research shows that although long-duration and short-duration exercises are similar in terms of energy expenditure, their impact on health indicators may not show significant differences, which supports the flexibility of exercise interventions [60]. Therefore, when designing exercise interventions, it is important to adjust the type, intensity, and frequency of exercise according to the individual's specific needs and gender differences to achieve the best results.

5. Conclusion and future prospects

5.1. Contributions of previous research in the field

Exercise, as a low-cost and easy-to-implement intervention, has been confirmed to effectively mitigate the negative impact of stress on tumor progression through various molecular mechanisms, while also significantly optimizing the psychological health and quality of life of cancer patients. Future research should continue to delve into optimal strategies for implementing exercise interventions and integrating them with personalized treatments to support better physical and psychological recovery for cancer patients. Exercise interventions not only serve as an adjunct to cancer treatment but also hold broad clinical applications, offering patients enhanced treatment outcomes and long-term health benefits.

5.2. Personalized design of exercise interventions

Given the variability in cancer types, stages, and patients' physical conditions, there are significant differences in the exercise intervention needs among patients. Future research should aim to develop personalized exercise prescriptions, tailoring exercise programs to the needs of each cancer patient. For instance, patients with limited physical function may benefit from low-intensity aerobic exercises or light resistance training, while those in better physical condition may engage in more challenging exercise programs. Moreover, patients at different stages of cancer may have varying tolerances to exercise: early-stage patients may handle higher-intensity exercise, while late-stage patients may require a greater focus on safety and rehabilitation exercises. By designing individualized interventions, exercise can better meet patients' specific needs, thereby optimizing their treatment outcomes and quality of life.

5.3. Synergistic effects of exercise and pharmacological therapies

A growing body of researches confirm that exercise not only serves as an independent non-pharmacological intervention but can also work synergistically with traditional treatments such as chemotherapy, radiotherapy, and immunotherapy.

Exercise can enhance the tumor microenvironment, improve immune cell function, inhibit inflammation and angiogenesis, and thereby increase the efficacy of drug therapies. For example, exercise can enhance the penetration of chemotherapy drugs, boost the cytotoxic effects of radiotherapy, and even optimize the outcomes of immunotherapy. Future research should further investigate the interaction mechanisms between exercise and pharmacological treatments, particularly the potential synergistic effects in regulating the tumor immune microenvironment, to determine the best combined exercise and drug therapy protocols.

5.4. Integrated application of exercise in psychological interventions

Exercise has a significant positive impact on the mental health of cancer patients, and future efforts should delve into combining exercise with psychological support therapies to form more comprehensive stress management strategies. By integrating exercise with psychological interventions, not only can anxiety and depression among cancer patients be alleviated, but their coping abilities can also be strengthened, optimizing treatment adherence and life satisfaction. This integrated approach can enhance patients' quality of life from both physiological and psychological perspectives. Future interventions should develop more combined models, incorporating exercise with psychological counseling, cognitive-behavioral therapy, and other psychological support methods to offer holistic treatment support for cancer patients.

Author contributions: Conceptualization, JK; methodology, XD and JK; validation, XD, FJ and JK; writing—original draft preparation, XD, RF and JK; writing—review and editing, XD, RF and JK; supervision, XD; project administration, XD; funding acquisition, XD. All authors have read and agreed to the published version of the manuscript.

Funding: 2021 Undergraduateucation and Teaching Reform Project of Shandong Province "Research on the Model of Integrated Education Inside and Outside of College Physical Education" (M2021107).

Acknowledgments: The language editing and optimization of this manuscript were supported by ChatGPT. Meanwhile, we would like to express our heartfelt gratitude to Dr. Jasmine Thompson, a native speaker, for her assistance in revising the grammar and expression of our manuscript.

Ethical approval: Not applicable.

Conflict of interest: The authors declare no conflict of interest.

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