Chen et al. World Journal of Surgical Oncology (2025) 23:192
https://doi.org/10.1186/s12957-025-03846-7

World Journal of Surgical Oncology

REVIEW

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Exercise therapy: an effective approach to mitigate the risk of cancer metastasis

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Abstract

Cancer metastasis is a primary contributor to cancer-related mortality, and mitigating the risk of metastasis has emerged as a central concern in oncology research. In recent years, exercise therapy, as a non-pharmacological intervention, has received considerable attention for its ability to enhance patients' quality of life and prognosis. Exercise significantly inhibits cancer spread, diminishes cancer risk, and improves therapy outcomes. Nonetheless, the exact mechanisms via which exercise inhibits the dissemination and metastasis of cancer cells are not fully elucidated. This review seeks to examine the mechanisms and prospective research avenues of exercise treatment in mitigating the risk of cancer metastasis. Moreover, it methodically examines pertinent clinical and scientific data, along with the efficacy of exercise therapies in real-world applications. The evaluation moreover suggests future research avenues, including a more profound exploration of mechanisms, the augmentation of clinical trials, the advancement of personalized and precision exercise therapy, and enhanced multidisciplinary collaboration. Exercise therapy shows significant potential in mitigating the risk of cancer metastasis, and its incorporation into holistic cancer treatment frameworks is advised to improve patients' general health and prognostic results.

Keywords Cancer, Exercise, Rehabilitation, Immunity, Metabolism, Cancer Metastasis, Review

Introduction

Despite notable progress in the management of primary tumors, addressing metastatic malignancies remains a significant clinical challenge [1, 2]. Conventional therapeutic modalities, including surgical resection, chemotherapy, and radiotherapy, demonstrate limited efficacy against metastases and are often accompanied by substantial adverse effects [3]. Although advancements in targeted therapies and immunotherapies have brought renewed optimism, these approaches face limitations such as tumor heterogeneity, treatment resistance, and immune-related side effects [4–6]. Metastasis persists as the leading cause of poor prognosis in cancer patients, driven by complex molecular mechanisms that enable cancer cells to spread and colonize distant organs [7]. Key processes include cancer cell invasion, angiogenesis, extracellular matrix degradation, immune evasion, and the establishment of a favorable tumor microenvironment (TME) [8–14] (Fig. 1).

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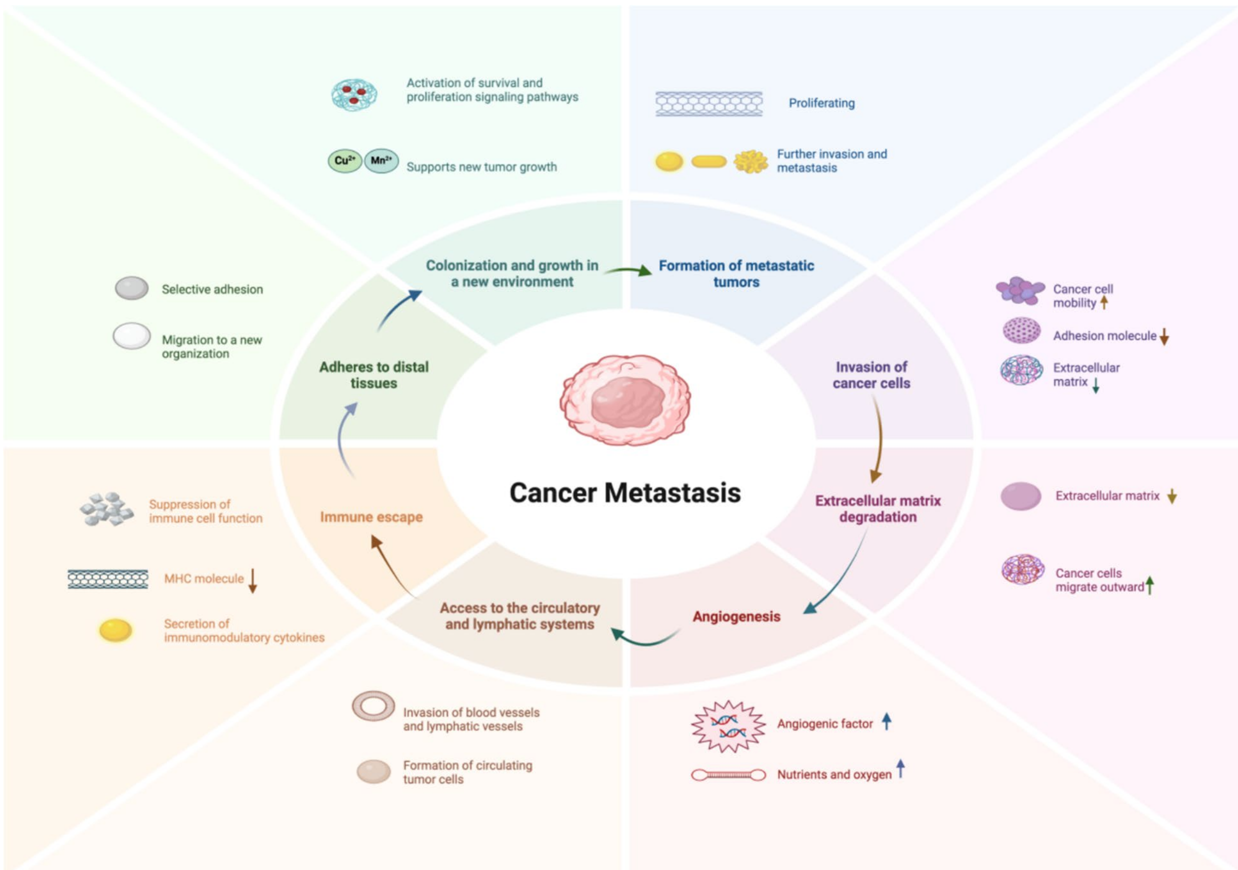

Fig. 1 Cancer metastasis involves a series of complex molecular events, including local invasion, intravasation, circulation, extravasation, and colonization at distant sites. The figure highlights key regulatory pathways and cellular interactions at each stage, providing an integrated overview of the metastasis process relevant to understanding potential exercise intervention points. *Created with BioRender.com*

In addition to medical interventions, lifestyle factors such as nutrition, mental health, and exercise have garnered increasing attention for their potential impact on cancer progression and outcomes [15]. Exercise therapy, a non-invasive and non-pharmacological intervention, has demonstrated significant benefits in managing chronic diseases like cardiovascular conditions, diabetes, and osteoporosis [16, 17]. In oncology, emerging evidence suggests that physical activity may influence tumor biology and reduce metastasis risk by enhancing immune function, modulating hormone levels, and suppressing inflammatory pathways [18–20]. The literature indicates that targeted exercise therapy is both feasible and safe when conducted under appropriate supervision. It demonstrates significant efficacy in improving eight key endpoints, including anxiety, depression, fatigue, quality of life, physical function, secondary lymphedema following breast cancer treatment, urinary incontinence, and post-mastectomy pain syndrome in breast cancer patients [21, 22]. Exercise has been shown to regulate immune responses, promote anti-tumor activity, and mitigate systemic inflammation, thereby influencing tumor growth and dissemination [23, 24]. Additionally, it can alter the TME by improving oxygenation, vascular remodeling, and metabolic conditions, potentially impairing cancer cell invasiveness [25–27].

While exercise therapy shows promise in reducing metastasis, its effects are not uniform across cancer types due to variations in tumor biology and metastatic patterns [28]. For instance, moderate-intensity aerobic exercise in breast cancer has been linked to enhanced immune surveillance and reduced tumor inflammation [29], while colorectal cancer may benefit from exercise-induced metabolic regulation and gut microbiota modulation [30]. In lung cancer, exercise appears to impact pulmonary vascular remodeling and boost anti-tumor immunity [31]. These cancer-specific differences highlight the need for tailored exercise protocols that account for distinct pathophysiological characteristics. Furthermore, patient-specific factors such as age, disease stage, and comorbidities further influence the efficacy of exercise interventions.

This review aims to provide a comprehensive overview of the impact of exercise therapy on cancer metastasis, focusing on its potential mechanisms of action, including immune modulation, inflammatory suppression, TME regulation, and hormonal and metabolic effects. Additionally, it explores the challenges of current research and identifies directions for future investigation to refine exercise interventions and optimize their application in oncology. By addressing the physiological variability among cancer types, this review seeks to offer insights that enhance metastasis management and improve long-term outcomes and quality of life for cancer patients.

Methodology for literature selection

This review is to deliver a thorough and impartial summary of the existing understanding of exercise treatment and its effects on cancer metastasis. While this is not a systematic review or meta-analysis, a methodical approach was employed to guarantee the incorporation of trustworthy, high-quality, and pertinent references. The procedure for selecting books is outlined below.

A comprehensive search of peer-reviewed literature was performed utilizing recognized academic databases, such as PubMed, Web of Science, and Google Scholar. The inquiry concentrated on publications published in English throughout the last decade (2015–2025) to guarantee the incorporation of contemporary perspectives. Keywords and phrases including "Cancer," "Exercise," "Rehabilitation," "Immunity," "Metabolism," and "Cancer Metastasis" were employed to discover papers pertinent to the impact of exercise on cancer metastasis. Studies were chosen for their pertinence to the review's primary issues, including those examining the correlation between exercise therapy and cancer metastasis. Preference was accorded to works utilizing rigorous experimental or observational methodologies, such randomized controlled trials (RCTs), cohort studies, or meticulously executed laboratory investigations. Moreover, research that provide innovative insights, synthesize existing evidence, or are produced by esteemed experts in the field, including review articles or consensus papers, were incorporated.

Studies were omitted due to substantial methodological deficiencies, such as limited sample numbers, absence of suitable control or comparison groups, or inadequate methodological reporting. Articles addressing subjects beyond the purview of this review or offering superfluous material without adding further value were excluded. Through the use of these inclusion and exclusion criteria, we guaranteed that the chosen studies were methodologically rigorous, pertinent to the review's aims, and facilitated a fair and informed discourse.

Since this is a general review, a narrative approach was employed instead of the methodical evaluation methods typical of systematic reviews or meta-analyses. This enabled the use of varied, high-caliber sources to promote an extensive and thorough discourse on exercise therapy and cancer metastasis. Simultaneously, identified deficiencies in the literature were recognized, and domains necessitating additional investigation were emphasized.

To uphold the reliability and relevance of the references, all research were rigorously assessed to guarantee their contribution to a well-informed and cohesive synthesis of the topic. This review synthesizes experimental data, clinical evidence, and expert evaluations to elucidate the current state of knowledge and offer significant suggestions for future research endeavors.

Mechanisms through which exercise affects cancer metastasis

Modulating the immune system

The immune system is essential for identifying and eradicating cancer cells, and its inhibition of cancer metastasis largely relies on the intricate synergistic interactions of many cells and chemicals [32]. Research has shown that physical exercise can significantly improve immune function, hence preventing the metastatic advancement of cancer [33]. Cytotoxic T lymphocytes (CTLs) are pivotal in inhibiting cancer spread. CTLs particularly identify aberrantly expressed antigenic molecules on the surface of neoplastic cells and directly eliminate them. Exercise has been demonstrated to enhance the proliferation and activation of CTLs, allowing for more efficient identification and targeting of cancer cells in the TME. Moreover, exercise amplifies the systemic anti-tumor actions of CTLs by augmenting their quantity and efficacy in the bloodstream, therefore impeding the spread of cancer cells from primary sites to remote areas [34]. Natural killer (NK) cells, an essential element of the innate immune system, are pivotal in inhibiting the proliferation and spread of cancer cells. Exercise has been demonstrated to markedly enhance both the quantity and cytotoxic function of NK cells [22]. NK cells can directly trigger apoptosis in neoplastic cells by releasing perforin and granzymes, thereby inhibiting future invasion and metastasis. Moreover, exercise promotes the release of pro-inflammatory cytokines, including interferon-γ, which activate NK cells and augment their cytotoxic efficacy. Augmented NK cell activity equips cancer patients with improved immune surveillance, facilitating the prompt eradication of possible micrometastases prior to their establishment [35].

Exercise can additionally foster the development of an anti-tumor milieu via modulating cytokine expression. Research indicates that physical activity stimulates the release of particular anti-tumor cytokines, including interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and interferon-γ (IFN-γ) [36]. These cytokines directly promote apoptosis in cancer cells and also alter the activity of immune effector cells, so augmenting their capacity to recognize and eradicate cancer cells. Furthermore, exercise diminishes the synthesis of pro-inflammatory cytokines, including interleukin-1 (IL-1) and interleukin-10 (IL-10), thus reducing the establishment of an immunosuppressive milieu and hindering cancer cells from circumventing immune surveillance [37]. Immunosuppressive elements in the TME frequently enable cancer cells to evade immune system identification, promoting their survival and dissemination. Exercise exerts regulatory effects on the immune system that transcend peripheral circulation and directly impact the TME. Exercise promotes the infiltration of effector immune cells and diminishes the activity of immunosuppressive cells, including regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), thereby enhancing the immune equilibrium within the TME and reinstating its anti-tumor efficacy [38, 39]. Furthermore, exercise enhances blood circulation and oxygen delivery, alleviating the hypoxic conditions within the TME. This consequently diminishes the secretion of pro-angiogenic molecules, thereby indirectly obstructing the distant spread of cancer cells [40].

The impact of exercise on the immune system has been thoroughly researched and validated. Moderate-intensity dynamic exercise, such as jogging or cycling for around one hour, can stimulate systemic immunological responses, prompting the mobilization of key leukocyte subsets, including NK cells, γδT cells, and CD8 + T cells, into peripheral circulation [41, 42]. NK cells are essential in anti-tumor immune responses by identifying and destroying aberrant tumor cells, whereas CD8 + T cells are distinguished for their antigen-specific cytotoxic function [43]. The preferential activation of these immune cell subsets following exercise enhances the anti-tumor immune response. Research has shown that exercise markedly enhances the activity of NK cells and CD8 + T lymphocytes, which are essential in tumor immunotherapy [44, 45]. The continuous activation of these immune effector cells is crucial for prolonging the survival of cancer patients. Additionally, skeletal muscles operate as endocrine organs during physical activity, modulating the immune system through the secretion of myokines [46]. Acute activity rapidly mobilizes a significant quantity of lymphocytes, but prolonged exercise training progressively augments the immune system's anti-tumor capabilities by facilitating the persistent mobilization and redistribution of effector cells [47]. Research indicates that while a solitary session of exercise can swiftly elevate the levels of NK cells in the bloodstream, its effect on NK cell infiltration within tumors is constrained. After several weeks of exercise training, a notable increase in NK cell infiltration within tumor tissues has been found, suggesting that sustained long-term exercise can augment the presence of anti-tumor effector cells at tumor locations, hence improving immune surveillance and tumor suppression [48]. Exercise not only directly enhances immune function but also positively affects cancer prevention and treatment via modulating the gut flora. Research indicates that physical activity enhances the prevalence of probiotics linked to reduced tumor growth and diminishes detrimental bacterial strains that facilitate tumor progression [49]. This indicates that physical activity impedes tumor progression not just by modulating immune cells but also by enhancing the gastrointestinal environment. For cancer patients, especially those with advanced-stage disease, suitable exercise programs can enhance immune function and increase survival rates [50]. Exercise therapy improves the mobilization, distribution, and activation of immune cells via intricate immunoregulatory systems, inhibiting cancer progression and metastasis [51]. Whether in cancer prevention or treatment, physical exercise demonstrates a powerful anti-tumor potential (Fig. 2).

Inhibition of inflammatory responses

The inflammatory response has a dual function in the onset and advancement of cancer. It can detect and eradicate cancer cells in the initial stages via immune surveillance mechanisms. Conversely, it may provide a conducive microenvironment for tumors during cancer progression, facilitating their proliferation and spread [52]. Exercise treatment, as a non-pharmacological intervention, can somewhat mitigate chronic inflammatory responses, therefore hindering cancer spread. Cancer metastasis often depends on a conducive milieu, with inflammation serving as a pivotal element of the TME [53]. Inflammation linked with tumors promotes angiogenesis, stromal remodeling, and immune evasion, therefore enhancing the survival, invasion, and metastasis of cancer cells. The inflammatory response enhances the proliferation and invasion ability of cancer cells by the secretion of pro-inflammatory cytokines, including IL-6, TNF-α, and interleukin-1 beta (IL-1β) [54]. Pro-inflammatory substances stimulate multiple signaling pathways in tumor cells, including the NF-κB and STAT3 pathways, therefore expediting malignant transformation and enhancing metastatic potential. Effectively suppressing inflammation diminishes the TME's supporting role for cancer cells, hence reducing the probability of metastasis. Exercise is acknowledged for its capacity to modulate inflammatory conditions in the body, namely by

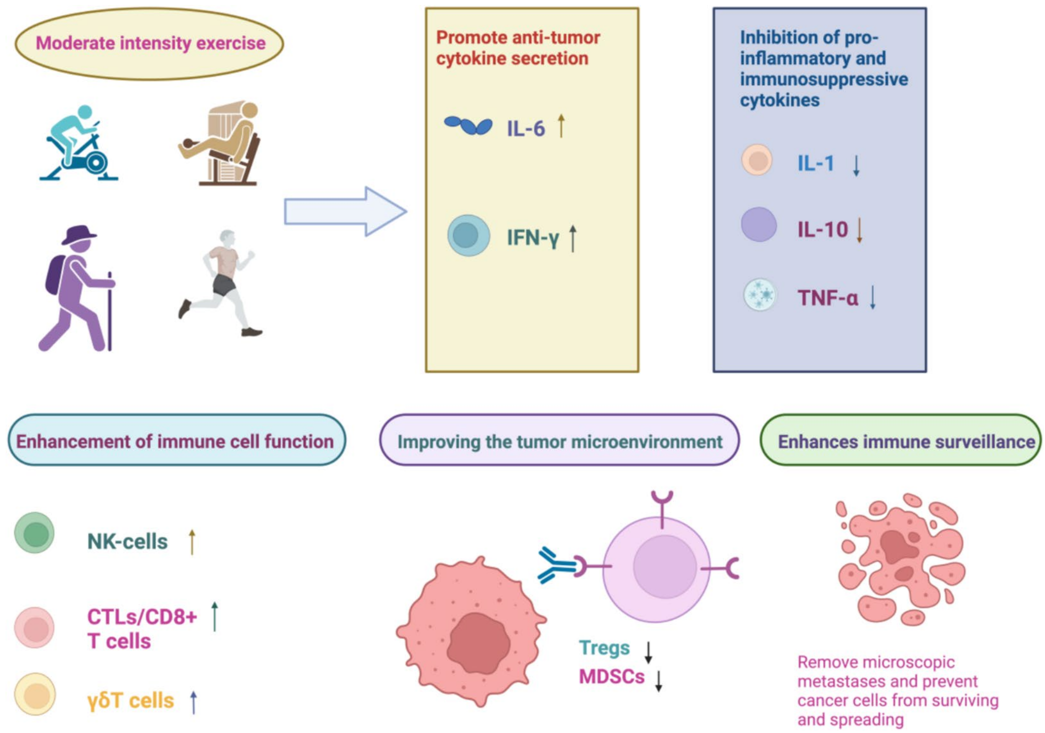

Fig. 2 Moderate exercise enhances the immune system's defensive capability against cancer cells by promoting the activity and recruitment of immune cells such as NK cells, T cells, and macrophages. This figure summarizes key mechanisms through which exercise-induced immune modulation may contribute to inhibiting cancer progression and metastasis. *Created with BioRender.com*

diminishing levels of certain pro-inflammatory cytokines [42]. During physical exertion, myokines such as IL-6, IL-7, and IL-15 are released in substantial amounts, with IL-6 exhibiting an exponential increase during exercise, attaining values significantly greater than baseline [55]. In addition to its role in metabolic control, IL-6 exerts anti-inflammatory effects by stimulating the release of anti-inflammatory cytokines, including IL-1 receptor antagonist (IL-1ra) and IL-10, while diminishing pro-inflammatory cytokines such as TNF-α [56]. It facilitates the secretion of additional anti-inflammatory cytokines, including IL-1 receptor antagonist (IL-1ra) and IL-10, while diminishing the concentration of the pro-inflammatory cytokine TNF-α, thus establishing a comprehensive anti-inflammatory milieu in the body [57]. This anti-inflammatory action alleviates chronic inflammation linked to cancer, inhibiting tumor growth induced by inflammation. Exercise-induced IL-6 interacts with NK cells, facilitating their swift mobilization into peripheral circulation and targeting of tumor locations [57]. This strategy amplifies the function of NK cells in tumor immune surveillance. Moreover, IL-7 and IL-15, critical cytokines significantly elevated during exercise, facilitate the production of naïve T cells, sustain T cell homeostasis, and regenerate new immune cell populations [58, 59]. IL-7 maintains thymic integrity, whereas IL-15 is essential for the survival, localization, and anti-tumor activities of NK cells [60, 61]. Chronic low-grade inflammation is a characteristic of aging and other chronic non-communicable disorders, such as cancer. This persistent inflammation facilitates carcinogenesis by encouraging the formation of immunosuppressive cells inside the TME [62]. Regular physical activity diminishes cancer risk by promoting the production of muscle-derived cytokines, sustaining a robust immune cell population, and mitigating chronic inflammation [63]. Exercise markedly diminishes the secretion of pro-inflammatory substances, hence attenuating the pro-metastatic inflammatory milieu of tumors and lowering the likelihood of cancer cell metastasis to remote organs through the vascular or lymphatic systems.

Furthermore, the anti-inflammatory response elicited by exercise can enhance immune system equilibrium and impede cancer cell proliferation by stimulating the release of anti-inflammatory cytokines, including IL-10 [37]. Macrophages, essential effector cells in the inflammatory response, significantly contribute to cancer growth. Tumor-associated macrophages (TAMs) can be polarized into pro-inflammatory M1 macrophages and anti-inflammatory M2 macrophages. Research indicates that M1 macrophages exhibit tumor-suppressive capabilities, while M2 macrophages facilitate tumor proliferation and spread. Exercise can modulate macrophage polarization by decreasing the quantity of M2 macrophages and enhancing the invasion of M1 macrophages. This modulation reduces pro-inflammatory cell presence in the TME and improves anti-tumor immune responses. Exercise diminishes the prevalence of M2 macrophages, effectively mitigating tumor-associated inflammatory responses and thereby reducing the probability of cancer cell spreading [64]. Oxidative stress is a principal catalyst of pro-inflammatory responses, and exercise can alleviate oxidative stress by augmenting antioxidant capacity. Oxidative stress increases the expression of pro-inflammatory proteins by activating signaling pathways like NF-κB and MAPK, hence sustaining inflammatory reactions [65]. Physical activity enhances the function of antioxidant enzymes, including superoxide dismutase (SOD) and catalase (CAT), hence diminishing oxidative stress and obstructing the activation of inflammatory signaling pathways [66]. This process inhibits the activation of pro-inflammatory responses, hence mitigating the pro-metastatic effects of the TME (Fig. 3).

Modification of the TME

Exercise modifies the TME via multiple pathways, hence reducing cancer spread. Recent research indicate that moderate exercise enhances hypoxia in tumor tissues and influences cellular and molecular mechanisms in the TME via intricate biological pathways, thus reducing tumor aggressiveness and spreading potential [67]. Exercise is essential in regulating hypoxia inside the TME. Hypoxia is a prevalent occurrence in tumors that intensifies malignancy and metastasis, as tumor cells exhibit increased invasiveness in low oxygen environments. Hypoxia stimulates angiogenesis, leading to aberrant vascular formations that disrupt blood flow, hence exacerbating the hypoxic condition of tumor tissues [40]. Moderate exercise can alleviate tumor hypoxia by enhancing overall blood circulation and optimizing vascular function. Certain studies indicate that aerobic exercise increases oxygen delivery to tissues, enhancing local oxidative conditions in tumors, which subsequently inhibits tumor cell proliferation and metastasis [68]. Exercise enhances vascular regeneration and normalizes blood circulation, hence diminishing hypoxia-induced vascular endothelial growth factor (VEGF) production in tumors and minimizing the development of aberrant blood vessels [69]. This not only restricts aberrant angiogenesis but also enhances the functionality of existing capillaries, facilitating improved oxygen and nutrient transport to the tumor location, and eventually inhibiting tumor cell viability and spread. The TME encompasses not only tumor cells but also many stromal cells,

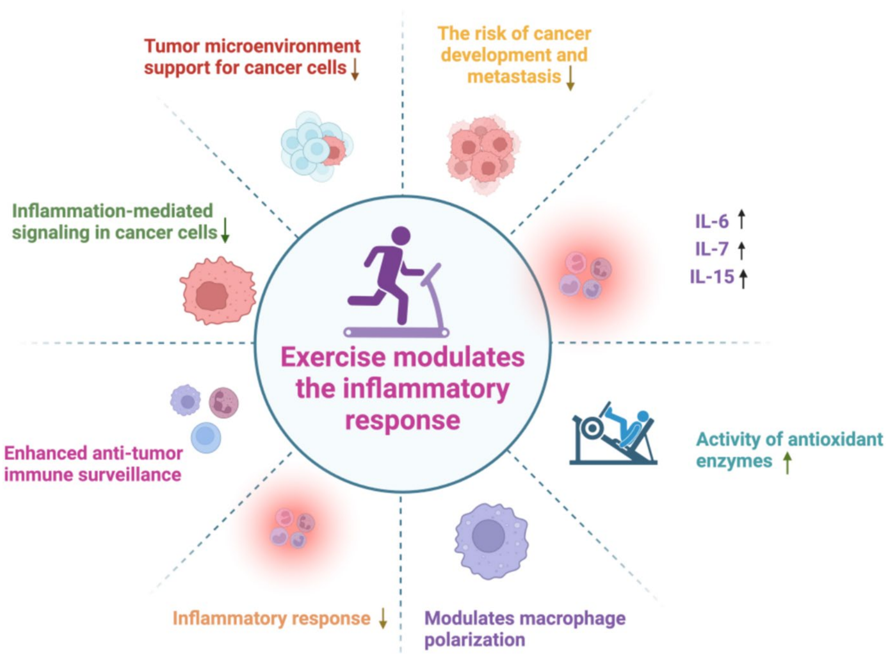

Fig. 3 Physical activity diminishes pro-inflammatory cytokine concentrations and enhances the expression of anti-inflammatory agents, thereby creating a systemic environment less conducive to tumor growth and metastasis. This figure illustrates the shift in cytokine balance resulting from regular exercise and its potential impact on cancer progression. *Created with BioRender.com*

including fibroblasts and immune cells [70]. Fibroblasts are essential in tumor progression and metastasis by secreting extracellular matrix (ECM) components and growth factors that facilitate tumor cell proliferation and invasion. Exercise suppresses fibroblast activity, diminishing ECM secretion and hence restricting tumor cell proliferation. Moreover, exercise influences the behavior of cancer-associated fibroblasts (CAFs), which facilitate tumor cell migration and invasion by altering the TME during metastasis. Exercise can inhibit the activity of CAFs, diminishing their supporting function in tumor growth [71]. Exercise promotes dendritic cell activation, augmenting their antigen-presenting capacities and consequently increasing the anti-tumor response of T cells [72].The immunoregulatory impact is essential for tumor management and the inhibition of metastasis. In addition to cellular and molecular mechanisms, exercise suppresses tumor metastasis by modulating the metabolism of the TME. Neoplastic cells frequently depend on glycolysis for energy generation. Moderate exercise can modify metabolic pathways in the body, changing the metabolic status of tumor cells. Exercise diminishes glucose absorption by tumor cells, consequently obstructing their energy procurement by glycolysis [73]. Furthermore, exercise enhances lactate metabolism, thereby decreasing the acidity of the TME, which subsequently inhibits tumor cell proliferation and spread. Studies indicate that an acidic TME increases the invasiveness and metastatic capacity of cancer cells [74]. Exercise, via modulating metabolic pathways, alleviates this detrimental TME, therefore limiting tumor cell spread [75].

Regulation of hormones and growth factors

Exercise greatly affects cancer metastasis by modulating hormone and growth factor levels in the body. Recent research has increasingly examined the effects of exercise on the endocrine system and the subsequent influence of these alterations on tumor growth and metastasis [76]. Physical activity has been demonstrated to reduce levels of insulin and insulin-like growth factor-1 (IGF-1) [77]. Increased concentrations of insulin and IGF-1 are significantly linked to a heightened risk of several malignancies, including breast, colon, and prostate cancers [78]. Insulin and IGF-1 stimulate tumor cell proliferation and metastasis by activating intracellular signaling pathways, including PI3 K/Akt and Ras/MAPK. Moderate exercise enhances insulin sensitivity and diminishes insulin resistance [79]. Exercise enhances glucose absorption by muscles, resulting in reduced insulin production and thus lower circulating insulin levels. Furthermore, physical activity decreases IGF-1 levels. Prolonged aerobic exercise has been demonstrated to markedly decrease plasma IGF-1 levels and elevate IGF-binding protein (IGFBP) concentrations, hence diminishing IGF-1 bioactivity [80]. These alterations may impede tumor cell growth and viability, hence diminishing the likelihood of cancer spread. Exercise also regulates sex hormone levels, specifically by reducing estrogen concentrations. Estrogen is instrumental in the progression of hormone-dependent neoplasms, including breast and endometrial malignancies. Elevated estrogen levels facilitate tumor cell growth and metastasis, while physical activity decreases estrogen levels via many pathways [81]. Exercise reduces adipose tissue, a significant source of estrogen, particularly in postmenopausal women. Conversely, exercise elevates levels of sex hormone-binding globulin (SHBG), which attaches to free estrogen, thereby diminishing its bioavailability. Epidemiological studies indicate a correlation between physical activity and reduced estrogen levels. Women participating in regular moderate-to-vigorous exercise demonstrate markedly reduced plasma estrogen levels relative to inactive counterparts, partially elucidating the preventive influence of exercise against breast cancer. Exercise may also influence several hormones, including testosterone and cortisol [82]. In males, moderate physical activity aids in the regulation of testosterone levels, potentially contributing to the prevention of prostate cancer. Cortisol, a stress hormone, is linked to immunosuppression and tumor advancement when persistently high [83]. Moderate exercise regulates cortisol secretion, mitigates stress responses, and may indirectly affect cancer spread. Physical activity influences adipokine concentrations, including leptin and adiponectin, released by adipose tissue. Leptin typically facilitates inflammation and tumor advancement, whereas adiponectin demonstrates anti-inflammatory and anti-tumor characteristics [84]. Obesity correlates with elevated leptin and diminished adiponectin levels, hence augmenting cancer risk. Exercise diminishes adipose tissue, resulting in decreased leptin levels and elevated adiponectin levels, which may impede tumor growth and metastasis [85]. Physical activity enhances glucose and lipid metabolism. Exercise diminishes blood glucose levels by improving muscle glucose uptake and utilization, hence restricting the sustenance that hyperglycemia offers to tumor cells [55]. Moreover, exercise affects lipid metabolism by decreasing blood lipid levels and diminishing lipid metabolic byproducts that activate tumor cells [86]. Moderate-intensity aerobic activities, including brisk walking, running, and swimming, are typically regarded as useful in producing anti-tumor effects.

Effects on cellular apoptosis and proliferation

Recent research have increasingly examined the impact of exercise on hormone and growth factor levels in the body, regulating tumor cell activity and consequently limiting cancer progression and metastasis [87]. In cancer, tumor cells frequently avoid apoptosis by downregulating pro-apoptotic proteins or upregulating anti-apoptotic factors. Studies demonstrate that moderate exercise can enhance the production of pro-apoptotic proteins, including p53 and Bax.p53, known as the "Guardian of the Genome," is crucial in the DNA damage response and apoptosis [88]. Research indicated that aerobic exercise training in murine models of breast cancer markedly elevated p53 expression in tumor tissues, resulting in increased apoptosis rates [89]. Likewise, Bax, a pro-apoptotic protein of the Bcl-2 family, might be enhanced by exercise, hence expediting apoptosis in neoplastic cells. Exercise decreases the amounts of anti-apoptotic agents [90]. Bcl-2, a pivotal anti-apoptotic protein, inhibits apoptosis, hence facilitating tumor proliferation and medication resistance. Research indicates that exercise reduces Bcl-2 expression, hence enhancing the susceptibility of tumor cells to apoptotic signals [91]. Research on colon cancer indicated that consistent running training markedly decreased Bcl-2 levels while increasing Bax expression in tumor tissues, leading to an elevated rate of apoptosis. This indicates that exercise modulates the Bcl-2/Bax ratio, promoting tumor cell death and inhibiting cancer growth [92]. Physical activity also influences the function of cell cycle regulatory proteins. Cell cycle dysregulation is a fundamental source of unrestrained tumor cell growth. Exercise disrupts essential cell cycle checkpoints, hence impeding tumor cell proliferation. Exercise diminishes the expression of Cyclin D1, inhibiting cells from progressing from the G1 phase to the S phase. Research indicated that aerobic exercise training in lung cancer mice markedly reduced Cyclin D1 levels in tumor tissues, hence diminishing cell proliferation rates [80]. Furthermore, exercise enhances the expression of cell cycle inhibitors like p21 and p27, which impede cell cycle progression and suppress tumor cell proliferation. Exercise influences apoptosis and proliferation by modulating hormone and growth factor levels. Hormones and growth factors are crucial in cellular signal transmission, directly influencing cell viability and proliferation. Exercise also regulates oxidative stress and inflammatory responses, so indirectly affecting apoptosis and proliferation. Oxidative stress and chronic inflammation are pivotal elements in tumorigenesis and advancement. Moderate exercise improves the body's antioxidant capacity, diminishes free radical generation, and decreases the chance of DNA damage. Studies indicate that exercise enhances the activity of superoxide dismutase (SOD) and glutathione peroxidase (GPx), hence safeguarding cells from oxidative damage [93]. Moreover, exercise reduces pro-inflammatory cytokines including tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β), alleviating the impact of inflammation on cell proliferation and death [94]. In summary, exercise exerts a complex, multifaceted regulatory effect on apoptosis and proliferation, profoundly influencing cancer spread. Exercise facilitates programmed tumor cell death by upregulating pro-apoptotic factors and downregulating anti-apoptotic proteins. It inhibits tumor cell proliferation by altering cell cycle regulatory proteins. Furthermore, by modifying hormone and growth factor concentrations, exercise diminishes pro-tumor signaling and amplifies anti-tumor effects (Fig. 4).

Clinical evidence of exercise therapy reducing cancer metastasis

Epidemiological studies

In recent years, a growing number of epidemiological studies have concentrated on the impact of exercise treatment in mitigating the risk of cancer metastasis. A substantial amount of research indicates that moderate physical exercise is strongly linked to enhanced outcomes in cancer patients. A study indicated that breast cancer patients who participated in moderate-intensity exercise post-diagnosis saw a markedly diminished risk of distant metastasis [95]. This longitudinal research of a substantial cohort of breast cancer patients shown that consistent aerobic exercise decreased the chance of metastases by 25%. These data underscore the potential preventive function of exercise in breast cancer therapy. Meyerhardt et al. presented a research in the Journal of Clinical Oncology that tracked colorectal cancer patients. The findings demonstrated that individuals who regularly engaged in aerobic exercise after surgery reported roughly a 30% decrease in the likelihood of cancer recurrence and metastasis. Researchers ascribed this to exercise-induced enhancements in immune function and decreases in inflammatory levels [96]. An epidemiological study on non-small cell lung cancer (NSCLC) patients indicated a substantial correlation between heightened physical activity post-diagnosis and enhanced disease-free survival. Researchers monitored over 500 NSCLC patients and discovered that those participating in 150 min of moderate-intensity exercise weekly exhibited a greater than 20% reduction in metastasis risk within three years post-diagnosis [97]. This indicates that exercise may impede the dissemination of cancer cells by altering the TME and inhibiting angiogenesis. A 2022 prospective study examined the impact of exercise on individuals with prostate cancer. Research indicated that patients engaging in 300 min or more of exercise weekly post-diagnosis exhibited a markedly lower risk of bone metastases [98].Researchers proposed that this is intricately linked to the regulatory effects of exercise on bone metabolism and the immunological milieu of the bone

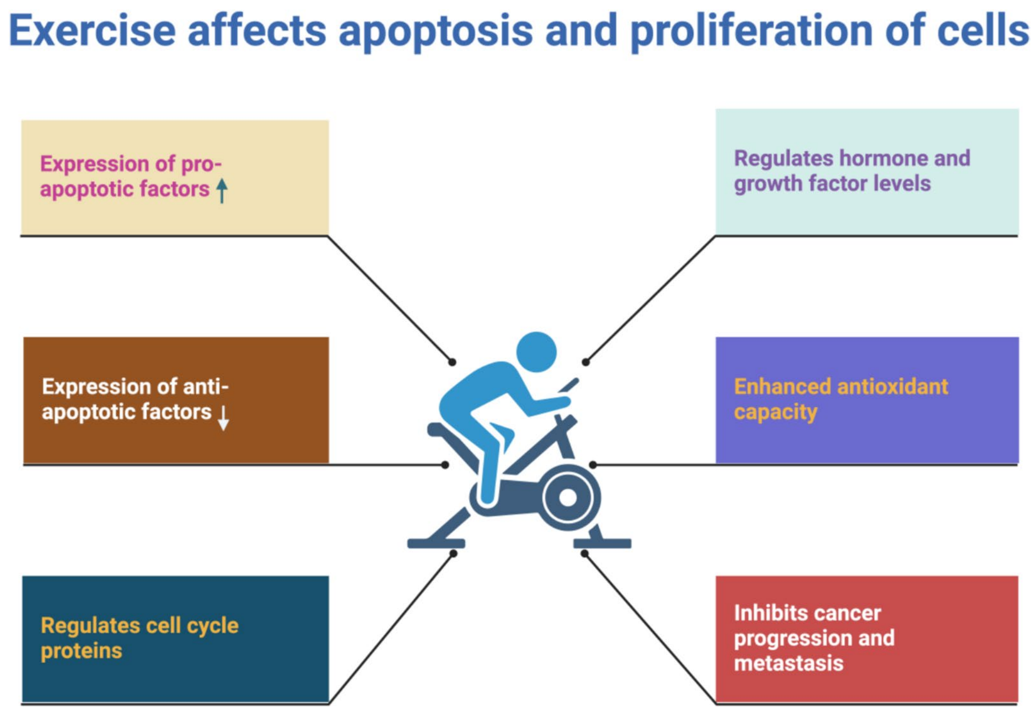

Fig. 4 Exercise promotes apoptosis in cancer cells and suppresses their growth by modulating signaling pathways involved in cell survival and programmed cell death. This figure illustrates how regular physical activity can activate pro-apoptotic factors and inhibit proliferative signals, thereby contributing to tumor suppression. *Created with BioRender.com*

marrow. These epidemiological studies offer substantial evidence endorsing the efficacy of exercise therapy in diminishing the risk of cancer metastasis.

Clinical trial studies

In recent years, there has been a consistent rise in clinical trials investigating the impact of exercise treatment on cancer patients. While direct clinical trials examining the function of exercise in mitigating cancer metastasis risk are scarce, current studies suggest that exercise enhances patient prognosis and postpones disease progression. This offers essential evidence for investigating the potential of exercise in reducing metastatic risk. Wang et al. evaluated the impact of a digital exercise intervention in a randomized controlled trial (RCT) comprising patients with metastatic prostate cancer. Results indicated that patients undergoing exercise therapies had substantial enhancements in quality of life and physical fitness, together with signs of decelerated illness development [99]. This indicates that exercise may contribute to postponing disease progression and diminishing the chance of metastasis.

Newton et al. investigated the impact of several exercise modalities on bone density in patients with prostate cancer. Their research indicated that weight training and specific workouts preserved spine and hip bone density, hence diminishing the risks of osteoporosis and bone metastases [100]. This is crucial for averting bone metastases in men with prostate cancer. Baumann et al. performed a multicenter randomized controlled trial examining the impact of exercise on prostate cancer patients receiving androgen deprivation therapy. The research demonstrated that exercise programs substantially mitigated treatment-related side effects, enhancing muscle mass and functional status [101]. This study did not directly assess metastasis risk; however, improved physical fitness may promote resilience against disease progression. In the CARE trial, Perrier et al. implemented exercise treatments alongside adjuvant chemotherapy for patients with breast cancer. The findings indicated substantial enhancements in physical fitness and quality of life within the exercise cohort, together with evidence suggesting diminished risks of disease recurrence and progression [102]. This highlights the possible significance of exercise in the therapy of breast cancer. Sabag et al. synthesized current evidence about the significance of exercise in cancer care in a published statement. The article highlighted that exercise enhances physical fitness and quality of life while potentially diminishing the risks of disease recurrence and metastasis [103]. This assertion reinforced the significance of exercise as an essential element of holistic cancer therapy. Although direct evidence necessitates additional research for validation, existing studies indicate favorable tendencies. Exercise, as a secure, economical, non-pharmacological intervention, merits extensive incorporation into the holistic therapy and rehabilitation of cancer patients.

Animal experimental studies

Animal experimental investigations have been essential in clarifying the processes by which exercise therapy diminishes the risk of cancer spread. Researchers can thoroughly examine the impact of exercise on cancer cell metastasis and its underlying mechanisms by replicating human malignancies in animal models. Koelwyn et al. found that consistent aerobic exercise suppressed lung metastases in a murine model of breast cancer. Their research indicated that exercise increased the activity of NK cells, hence diminishing the metastatic potential of cancer cells [104]. This discovery underscores the significance of the immune system in the anti-tumor actions facilitated by exercise. In a melanoma murine model, Pedersen et al. discovered that physical activity suppressed cancer cell proliferation and spread via altering the TME. Exercise specifically diminished the expression of pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), hence enhancing immunological responses [44]. Dethlefsen et al. posited that exercise-induced myokines, including interleukin-6, can directly influence cancer cell proliferation and migration. Exercise may suppress the invasiveness and metastatic potential of cancer cells by activating intracellular signaling pathways [105]. Hojman et al. consolidated findings from many animal research, highlighting the integral role of exercise in modulating immune function, inflammatory responses, and the TME. It was proposed that exercise may inhibit cancer growth and metastasis via various synergistic mechanisms [20]. These animal studies illustrate the considerable potential of exercise therapy in mitigating the risk of cancer spread.

Discrepant evidence and determinants affecting exercise therapy results

Exercise treatment has been thoroughly investigated for its efficacy in reducing cancer metastasis. A multitude of research has demonstrated encouraging outcomes, including improved immune surveillance and less metastatic burden. Betof et al. and Hojman et al. found that exercise-induced mobilization of T cells and NK cells dramatically diminished tumor growth and metastasis in preclinical breast cancer models [20, 106]. Nevertheless, contradictory results can also present. Taaffe et al. found no significant impact of exercise on metastases in prostate cancer patients [107], however Pedersen et al. noted minimal advantages in aggressive melanoma models [44]. These inconsistencies may stem from heterogeneity in study designs, including changes in exercise style, intensity, and duration, alongside variances in cancer type, tumor biology, and patient-specific variables. Table 1 summarizes significant studies, elucidating supportive and contradicting findings along with potential explanations contributing to these discrepancies.

Practical strategies for exercise interventions

Selection of exercise types

Choosing the suitable form of exercise is essential for attaining maximum effectiveness in exercise therapies for cancer patients. Diverse forms of exercise exert distinct effects on patients' physiological functions, immunological systems, and mental health. Recent studies demonstrate that a multifaceted intervention incorporating several exercise modalities might significantly diminish the risk of cancer metastasis and enhance patients' quality of life [110]. Aerobic activity, including walking, running, swimming, and cycling, improves cardiovascular

Table 1 Summary of key studies on exercise therapy and cancer metastasis

Study	Cancer Type	Exercise Type	Outcome	Key Findings
Betof et al. [106]	Breast cancer (mice)	Aerobic (treadmill)	↓ Tumor growth & metastasis (↑ T-cell activity)	Exercise enhances immune function and reduces lung metastasis
Hojman et al. [20]	Breast cancer (mice)	Aerobic (voluntary)	↓ Metastatic burden (↑ NK-cell mobilization)	Exercise induces systemic immune activation in preclinical models
Taaffe et al. [107]	Prostate cancer	Mixed (aerobic + RT)	No significant reduction in metastasis rates	Cancer type may influence exercise efficacy
Pedersen et al. [44]	Melanoma (mice)	Aerobic (treadmill)	No reduction in metastatic progression	Exercise impact depends on tumor aggressiveness and biology
Schmitz et al. [108]	Breast cancer	Moderate aerobic	↑ Survival rates & ↓ recurrence risk	Clinical evidence supports moderate exercise benefits
Courneya et al. [109]	Colorectal cancer	Aerobic (walking)	↑ QoL, ↓ inflammatory markers	Exercise improves inflammatory and metabolic profiles in patients

function and promotes immunity. Research conducted by Brown et al. indicates that aerobic exercise diminishes fatigue and enhances sleep quality in breast cancer patients [111]. Moreover, aerobic activity reduces inflammation and enhances prognosis. Resistance training, designed to enhance muscle strength and endurance, encompasses weightlifting, resistance band workouts, and bodyweight training. The work by Zimmer et al. demonstrates that resistance training enhances muscle mass and mitigates treatment-induced muscular atrophy in cancer patients [112]. This is favorably correlated with mitigating cancer-related fatigue and decreasing the likelihood of metastasis. High-Intensity Interval Training (HIIT) involves alternating between vigorous activity and brief rest intervals. Devin et al. discovered that HIIT surpasses moderate-intensity continuous training in enhancing cardiac function and physical fitness among colorectal cancer survivors [113]. Moreover, HIIT may impede tumor proliferation by modulating metabolic pathways. Flexibility activities, like yoga and tai chi, enhance joint mobility and alleviate discomfort. Tai Chi, often spelled "Taiji," is an ancient Chinese mind–body discipline that combines slow, intentional movements with deep respiration and mental focus. Tai Chi, once conceived as a martial art, is today extensively practiced for its health advantages, such as enhancing physical balance, flexibility, and mental wellness. Tai Chi routines generally comprise a sequence of fluid, meditative motions that prioritize posture control, body alignment, and harmonic motion [114]. Cramer et al.'s systematic study indicates that yoga markedly enhances the quality of life for breast cancer patients and mitigates anxiety and depression [115]. Balance training aids in fall prevention and is especially appropriate for senior individuals [116]. Core strength training refers to a type of exercise that targets the muscles in the central part of the body, collectively known as the "core." The core encompasses the muscles of the abdomen, lower back, pelvis, and hips, which work together to stabilize the spine and support overall body movement [117], which is vital for enhancing patients' quality of life [118]. Functional training, which denotes a sort of exercise aimed at enhancing the execution of daily tasks by replicating real-life movements. In contrast to conventional weightlifting or isolated muscle workouts targeting individual muscle groups, functional training prioritizes the collaboration of several muscle groups to improve balance, coordination, strength, and flexibility. This training is especially advantageous for enhancing movements like bending, lifting, pushing, pulling, twisting, and walking—activities vital for daily life. Studies indicate that functional training enhances swallowing capabilities and overall quality of life in individuals with head and neck cancer [119]. Aquatic exercise, leveraging water's buoyancy to alleviate joint stress, is appropriate for individuals with joint disorders or obesity [120]. The study by Siqueira et al. demonstrates that water training enhances upper limb functionality and diminishes lymphedema in breast cancer patients [121]. Formulating individualized exercise regimens tailored to patients' physical conditions and preferences may yield superior outcomes. Hayes et al. highlighted that the incorporation of aerobic exercise, weight training, and flexibility exercises can significantly enhance overall health [122]. When selecting exercise modalities, it is imperative to consider patients' medical histories, fitness levels, and stages of treatment. A thorough evaluation by the medical team can facilitate the development of a secure and practical workout regimen [123]. Integrating diverse exercise modalities customized to personal requirements mitigates the risk of cancer spreading and improves overall health.(Table 2).

Exercise intensity and frequency

In exercise therapies for cancer patients, appropriately calibrating exercise intensity and frequency is essential for maximizing intervention efficacy and ensuring

Table 2 Attributes of various exercise modalities

Type of exercise	Characteristic	Cancer type and stage
Aerobic exercise	Enhances cardiorespiratory fitness, boosts immunity and reduces inflammation levels	Breast cancer, Stage I-II [121, 124]
Resistance training	Increase muscle strength and endurance, improve muscle mass	Head and neck cancer, Stage I-IV [112, 120, 125]
HIIT	Regulates metabolic pathways and inhibits tumor growth	Lung cancer, Stage I-II [113, 126]
Flexibility Exercise	Improves joint mobility, reduces pain, reduces anxiety and depression	Breast cancer, Postoperative [115, 127]
balance training	Prevents falls, especially for elderly patients	Colorectal cancer, Stage III-IV [111, 128]
Core Strength Training	Focus on the muscles of the abdomen, reduce lower back pain	Breast Cancer, Stage I-II [129]
functional training	Improve self-care skills by imitating daily life actions	Geriatric oncology, Entire stage [130]
Aquatic exercise	Utilizes the buoyancy of water to reduce stress on joints, suitable for patients with joint problems or obesity	Colon cancer, Stage III [131]

patient safety. Recent research and global guidelines highlight that personalized exercise prescriptions might enhance patients' physical and mental well-being [132]. Exercise intensity must be tailored to the patient's physical condition, disease stage, and treatment regimen. Moderate-intensity aerobic exercise is typically regarded as safe and helpful for the majority of cancer patients [133]. Moderate intensity is characterized as 64% to 76% of the maximum heart rate or a felt exertion rating (RPE) of 12 to 13 on a 6–20 scale [134]. Moderate intensity is advised for resistance training, corresponding to 60% to 70% of one repetition maximum (1RM) [135], with 8 to 15 repetitions per major muscle group throughout 1 to 3 sets [136]. Individuals with inferior strength or novices in resistance training may utilize lower intensities, ranging from 40 to 50% of their 1RM [137]. Cancer patients are often advised to participate in a minimum of 150 min of moderate-intensity aerobic exercise or 75 min of high-intensity aerobic exercise each week. This can be segmented into sessions lasting 30 to 60 min, occurring 3 to 5 days weekly [133]. Resistance exercise is recommended 2 to 3 times per week, with rest days interspersed between sessions [136]. Individuals initiating an exercise regimen or possessing poor fitness levels may accrue segmented exercise sessions of 10 min throughout the day to progressively enhance their daily activity levels. Enhancing physical activity in everyday routines and minimizing inactive periods are advantageous as well [132]. Individualization is the fundamental idea in assessing exercise intensity and frequency. Modifications must be implemented according to the patient's physical state, therapy advancement, and individual preferences [138]. Frequent evaluations of patients' fitness and health conditions, along with prompt modifications to exercise prescriptions, improve the efficacy of interventions [139]. Exercise regimens must meticulously observe patient reactions, including exhaustion, pain, and discomfort [137]. In the event of any adverse responses, exercise intensity and frequency must be rapidly modified, or exercise should be halted [135]. Appropriately determining exercise intensity and frequency is crucial for the efficacy of exercise therapies for cancer patients. Individualized exercise prescriptions, along with scientific monitoring and changes, can optimize patients' quality of life and rehabilitation outcomes.

Exercise intervention strategies for different metastatic sites

Exercise therapy serves as an adjuvant strategy in the treatment and rehabilitation of cancer patients, positively impacting quality of life, increasing immunity, reducing symptoms, and decelerating disease progression. Nonetheless, the diverse metastatic locations of cancer necessitate variations in suitable exercise types and intensities. Bone metastases render patients susceptible to fractures and additional problems due to the fragility of the bones. Low-impact activities, including walking, swimming, and mild stretching, are advised to reduce the incidence of fractures. Recent studies indicate that moderate strength training, conducted under professional supervision, might enhance muscle strength, decrease bone stress, mitigate discomfort, and increase stability [140]. Pulmonary metastases frequently result in symptoms such as dyspnea and tiredness. Suitable aerobic activities (e.g., jogging, cycling, and swimming) are thought to improve cardiopulmonary function, augment endurance, and diminish weariness. Recent studies indicate that consistent low-intensity aerobic exercise enhances pulmonary function, diminishes dyspnea, and elevates quality of life [141]. The liver, as an essential metabolic organ, restricts exercise tolerance in patients with liver metastases who are susceptible to tiredness. Exercise therapy ought to include low-intensity, brief-duration activities like yoga and tai chi to alleviate liver strain and enhance circulation. Smith et al. assert that simple stretching activities may reduce discomfort in the hepatic region and enhance general health [142]. Patients with brain metastases frequently encounter cognitive deterioration and balance impairments, rendering safety and cognitive enhancement essential objectives in exercise therapies. Balance training, such as standing balance exercises and gait training, together with light cardiovascular workouts like stationary cycling, can improve balance and cognitive function. Wälchli et al. demonstrate that exercise therapy, when paired with cognitive training, significantly mitigates cognitive decline and enhances patients' autonomy in everyday activities [143]. Lymph node metastases frequently occur alongside lymphedema, especially prevalent in post-mastectomy patients. Moderate resistance and stretching activities can facilitate lymphatic fluid flow and reduce limb edema. A thorough evaluation by Lin et al. indicates that resistance training significantly diminishes the risk of lymphedema and enhances upper limb mobility [144]. Patients with skin metastases exhibit weak skin that is susceptible to damage [145]. Exercises that minimize friction or excessive stretching are advised, including tai chi and restorative yoga. These activities facilitate circulation, bolster immunity, and reduce skin irritation or injury. Gastrointestinal metastases are linked to symptoms such as dyspepsia and diminished physical strength. Exercise therapies have to emphasize low-to-moderate intensity aerobic activities and modest resistance training to enhance gastrointestinal motility and facilitate digestion [146]. Oliveira et colleagues. discovered that moderate aerobic exercise enhances digestive system functionality and alleviates abdominal discomfort associated with dyspepsia [147]. The selection of exercise therapy for various metastatic locations must be personalized to guarantee safety and efficacy. (Table 3).

Application of new technologies and equipment

The integration of novel technology and gadgets in exercise intervention strategies has emerged as a crucial method for enhancing precision and tailoring therapies to individual needs. Advancements in technology have led to the introduction of numerous revolutionary instruments in exercise therapy, aimed at improving the efficacy of exercise therapies for cancer patients in a more efficient, safe, and precise manner. These technologies enhance the efficacy of therapies and furnish credible evidence for real-time monitoring and personalized modifications. Wearable gadgets, such smart wristbands, heart rate monitors, and accelerometers, can monitor physiological data such as heart rate, exercise volume, step count, and calorie expenditure in real-time during exercise interventions [148]. The data can be wirelessly communicated to healthcare professionals' monitoring systems, allowing the medical team to remain informed of patients' exercise state and implement timely interventions and changes. Furthermore, remote monitoring technologies enable healthcare providers to assist cancer patients in home-based rehabilitation, minimizing hospital visits while improving treatment continuity and adherence [149]. Virtual reality (VR) technology offers cancer patients realistic exercise experiences by mimicking several scenarios, including outdoor strolling, yoga sessions, and gym workouts, so enhancing their engagement and motivation while mitigating exercise weariness and psychological stress. Cancer patients can participate in walking workouts within a virtual outdoor setting, relishing picturesque vistas without limitations imposed by weather or geography. Augmented reality (AR) superimposes virtual navigation information over the actual world. During strength training, augmented reality (AR) can provide immediate feedback on posture correction, assisting patients in sustaining correct exercise positions and preventing injuries [150]. Artificial intelligence (AI) technologies can formulate personalized exercise prescriptions tailored to patients' physiological parameters, cancer types, disease stages, and individual preferences. AI algorithms analyze comprehensive patient data to determine optimal combinations of exercise intensity, frequency, and types for various cancer patients, dynamically adjusting intervention tactics based on real-time feedback and physical conditions [151]. Machine learning algorithms can anticipate patients' exercise tolerance and recovery progress, allowing healthcare providers to create more accurate and successful exercise schedules [152]. The Internet of Things (IoT) consolidates diverse smart devices, including fitness equipment, smart scales, and blood oxygen monitors, into a cohesive health management system, facilitating thorough monitoring of exercise intervention outcomes via interconnected data [153]. For example, during home workouts using fitness equipment,

Table 3 Exercise intervention strategies for different metastatic sites

Metastatic sites	Common symptoms	Type of exercise	Relevant research
Bone metastasis	Fragile bones, susceptible to fractures and complications	Low-impact exercise (walking, swimming, gentle stretching); moderate strength training under professional supervision	Moderate strength training strengthens muscles, reduces bone load, relieves pain and improves stability [140]
Lung metastasis	Difficulty breathing, fatigue	Appropriate aerobic exercise (jogging, cycling, swimming)	Regular low-intensity aerobic exercise improves lung function, reduces dyspnea and improves quality of life [141]
Liver metastasis	Low exercise tolerance and fatigue	Low intensity, short duration exercise (yoga, Tai Chi)	Light stretching relieves liver area discomfort and promotes overall health [142]
Brain metastasis	Cognitive decline, balance disorders	Balance training (standing balance exercises, gait training); light aerobic exercise (stationary bike riding)	Exercise therapy combined with cognitive training slows cognitive deterioration, increases independence in life [143]
Lymphatic node metastasis	lymphoedema	Moderate resistance exercises, stretching exercises	Resistance exercise reduces risk of lymphedema and improves upper extremity mobility [144]
Skin metastasis	Fragile and vulnerable skin	Low-intensity exercise such as Tai Chi and gentle yoga; avoid friction or strenuous stretches	Promotes blood circulation and strengthens immunity without causing excessive skin irritation [145]
Gastrointestinal metastasis	Indigestion, loss of energy	Low to moderate intensity cardio, light resistance training	Moderate aerobic exercise helps improve digestive function and reduce abdominal discomfort [147]

patients' physical performance data can be transmitted to the cloud in real-time, enabling doctors and caregivers to remotely oversee performance and offer prompt feedback. This multi-device integration and data-sharing system provides strong data support for tailored and accurate workout programs.3D printing technology significantly contributes to exercise therapy, particularly for patients needing assistive aids during cancer rehabilitation [154]. In postoperative rehabilitation for breast cancer patients, 3D printing can create customized exercise aids, including supporting braces or adjustable weight-bearing devices, designed to meet the individual requirements of each patient. The exceptional flexibility and accuracy of 3D printing guarantee that the equipment conforms closely to patients' anatomical features, hence improving comfort and safety during rehabilitation [155].

These technological methods enhance exercise interventions and bolster healthcare providers' monitoring and supervision abilities, ultimately offering cancer patients an improved rehabilitation experience. As technology progresses, increasingly inventive methods will be implemented in exercise treatments, providing enhanced opportunities and elevated levels of individualized services in cancer treatment and recovery.

Discussion

Potential synergies between exercise and conventional cancer treatments

The role of exercise therapy in cancer care extends beyond its independent effects on tumor progression and metastasis. Increasing evidence suggests that exercise may interact synergistically with conventional cancer treatments, such as chemotherapy, radiation, and immunotherapy, enhancing their efficacy or mitigating their adverse effects. These potential interactions represent a promising area of research that warrants further exploration.

For chemotherapy, preclinical studies indicate that exercise may improve drug delivery to tumors by enhancing blood flow and vascular perfusion [156, 157]. This effect not only facilitates more efficient drug delivery but may also potentiate the cytotoxic effects of chemotherapeutic agents [158]. Moreover, exercise interventions have been reported to alleviate common chemotherapy-related side effects, including fatigue, nausea, and neuropathy, thereby improving patient adherence to treatment regimens and overall quality of life [159, 160]. Similarly, exercise has been proposed as a potential adjunct to radiation therapy [85]. Recent studies suggest that exercise may attenuate radiation-induced inflammation and oxidative stress, as well as mitigate radiation-associated fatigue [161]. These effects are thought to arise from exercise-induced systemic adaptations, such as enhanced mitochondrial function and reduced pro-inflammatory cytokine production [162]. While further research is needed to clarify dose–response relationships, early findings indicate that exercise may improve the tolerability of radiation therapy while maintaining or enhancing its therapeutic effects. In the context of immunotherapy, exercise has shown promise in modulating the immune system to create a more favorable tumor microenvironment [85].

Despite this growing body of evidence, the interactions between exercise and conventional cancer treatments remain underexplored in clinical settings. Key gaps include a lack of standardized exercise protocols optimized for synergy with specific treatments, limited understanding of the timing and intensity of exercise relative to treatment schedules, and insufficient consideration of patient-specific factors such as age, comorbidities, and treatment-related toxicities. Addressing these challenges will require well-designed clinical trials that evaluate the safety and efficacy of combined exercise and treatment regimens while incorporating biomarkers to better understand the underlying mechanisms.

The role of exercise in addressing cachexia and anorexia in cancer patients

Cachexia and anorexia represent common and severely debilitating complications in patients with advanced cancer, particularly those with metastatic disease. Cachexia is characterized by involuntary weight loss, muscle wasting, and systemic inflammation, whereas anorexia is marked by a loss of appetite and reduced food intake. These conditions are closely intertwined and significantly contribute to increased morbidity, diminished quality of life, and poor prognosis in cancer patients [163, 164].

Emerging evidence suggests that exercise interventions may alleviate both cachexia and anorexia through multiple mechanisms. Regular physical activity has been demonstrated to enhance muscle protein synthesis and inhibit proteolysis, thereby counteracting the muscle wasting associated with cachexia [165, 166]. Exercise also modulates systemic inflammation by reducing levels of pro-inflammatory cytokines (e.g., TNF-α, IL-6) and promoting the release of anti-inflammatory mediators, which may further slow the progression of cachexia [167, 168]. Moreover, studies indicate that exercise can influence appetite regulation by potentially stimulating orexigenic pathways, such as ghrelin secretion, and improving food intake in cancer patients experiencing anorexia [169, 170].

Clinical trials and observational studies provide support for the beneficial effects of tailored exercise programs in mitigating the adverse impacts of cachexia and anorexia, with improvements observed in physical function, nutritional status, and overall quality of life [171–173]. However, the optimal type, intensity, and duration of exercise for this patient population remain unclear, highlighting the need for further research into personalized exercise prescriptions that account for the severity and stage of cachexia and anorexia. In summary, integrating exercise into the multidisciplinary management of cancer patients offers a promising strategy to address cachexia and anorexia, ultimately enhancing patient outcomes and quality of life.

Challenges and prospective research directions

This study highlights the potential benefits of exercise therapy in clinical oncology while addressing its limitations and proposing future research directions. A key challenge lies in the variability of findings across studies, stemming from differences in study design, sample sizes, and methodologies. While some research reports notable improvements in patient outcomes, others observe limited effects, indicating the need for large-scale, RCTs with standardized procedures and extended follow-up durations to derive more consistent and reliable conclusions [174]. Additionally, individual differences in response to exercise therapy—shaped by factors such as age, gender, genetic predisposition, physical condition, and pre-existing comorbidities—add complexity to the development of universally applicable exercise regimens [22]. For example, elderly patients or those with advanced disease stages may respond differently compared to younger or healthier individuals, while comorbidities such as diabetes or cardiovascular disease could influence the feasibility or effectiveness of certain exercise protocols.

The intensity of exercise is another important factor requiring further investigation. Moderate-intensity exercise has been associated with reductions in tumor growth and improvements in quality of life, whereas high-intensity regimens may, in some cases, yield less favorable effects, potentially influencing tumor progression via stress hormone elevation or inflammatory pathways [175]. This underscores the importance of tailoring exercise programs to individual patient characteristics and carefully managing intensity levels in clinical practice. Furthermore, the molecular mechanisms underlying the effects of exercise on tumor progression and metastasis remain insufficiently explored. Current evidence suggests that exercise may modulate the TME by enhancing immune responses, reducing inflammation, and promoting angiogenesis [80, 176, 177]. However, the specific biological processes involved, as well as the distinct impacts of aerobic versus resistance training, require further elucidation. In certain contexts, high-intensity exercise may be associated with unintended effects on tumor growth or metastasis, highlighting the need for additional research to clarify these observations [178].

To address these limitations, future studies should prioritize the implementation of large-scale RCTs with diverse and representative patient populations, standardized protocols, and prolonged observation periods to improve statistical power and generalizability. Furthermore, more precise stratification of patients based on demographic, clinical, and molecular profiles is essential for designing personalized exercise interventions that maximize therapeutic efficacy. A deeper investigation into the molecular pathways through which exercise influences cancer progression is also important to ensure the safety, scientific validity, and clinical applicability of exercise therapies. Resolving these research gaps will contribute to the broader integration of exercise therapy into oncology, enhancing outcomes for a wider range of cancer patients [179].

Conclusion

This study highlights the efficacy of exercise therapy in reducing the risk of cancer metastasis through many pathways, such as immunological modulation, inflammation reduction, and angiogenesis regulation. However, it is important to recognize that the impact of exercise on metastasis is highly context-dependent and varies significantly based on factors such as cancer type, stage, metastatic location, and individual patient characteristics. Nevertheless, existing evidence is limited by methodological constraints, including small sample sizes, brief follow-up durations, and inadequate consideration of individual variability across cancer types, metastatic locations, and patient demographics. Preclinical results indicate that aerobic and resistance training may offer context-dependent advantages; yet, apprehensions remain about the paradoxical consequences of exercise in some circumstances. Future research should emphasize large-scale randomized trials with prolonged follow-ups to define dose–response relationships and metastasis-specific outcomes, while incorporating multi-omics strategies to understand molecular pathways. Simultaneously, tailored exercise protocols—differentiated by cancer biology, host characteristics, and treatment circumstances—must be established to enhance efficacy and safety. Rectifying these deficiencies will enhance exercise treatment as a scientifically validated complement in metastasis prevention, connecting translational knowledge with clinical application.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12957-025-03846-7.

Supplementary Material 1.

Authors' contributions

Xiaoyan Chen: Writing-original draft, Conceptualization. Junfeng Zhang: Writing-original draft, Conceptualization. Feng Gao: Writing-review & editing. Na Liu：Writing-review & editing. Huijun Du: Writing- review & editing. Jiuhu Li: Writing- review & editing. Zhi Li: Writing-review & editing, Supervision. Rong Chen: Writing-review & editing, Supervision. All authors read and approved the final manuscript.

Funding

None.

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Competing interests

The authors declare no competing interests.

Received: 29 November 2024 Accepted: 6 May 2025
Published online: 16 May 2025

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