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Exercise therapy: Anti-tumor and improving chemotherapy efficacy

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ABSTRACT

The extant research evidence indicates that sensible exercise has a beneficial impact on the prevention and treatment of cancer. This paper presents a comprehensive literature review of the field of sports oncology. Its objective is to synthesize and analyze the impact of exercise training on cancer, as well as to elucidate the mechanisms through which exercise affects cancer progression. Additionally, it offers valuable insights for advancing fundamental and clinical research in sports oncology. Firstly, this paper provides a summary of the relationship between exercise and various aspects of tumor progression, including tumor size, weight, metastasis, tumor vascularity, myokine production, immune response, and the efficacy of cancer chemotherapy. Secondly, due to the diversity of tumor properties, we also explore the fact that the specificity of exercise prescription should be tailored to the different tumor types and patient profiles. Furthermore, we discuss the importance of considering individual differences when determining the type of exercise, intensity, intervention, and duration of exercise. Finally, this paper emphasizes the necessity of evaluating the interaction between exercise and conventional or novel immunotherapies and pharmacodynamics in future preclinical studies.

1. Introduction

Cancer is the primary or secondary cause of death for individuals under 70 in 91 out of 172 countries. Furthermore, in 22 additional countries, it ranks as the third or fourth leading cause of death for this age group.[1] Some studies have found that roughly two-thirds of all cancer cases result from random errors occurring during DNA replication.[2] Virus infections also play a significant role in the development of cancer. Additionally, lifestyle factors, such as smoking, overeating, and inactivity, contribute to the onset and progression of the disease.[3] Changing these unhealthy behaviors may help prevent or delay the onset of cancer. Numerous observational studies conducted over the past three decades have shown that long-term exercise can significantly reduce the risk of developing various types of cancer.[4] For example, a study showed that high doses of vitamin D, omega-3 and a simple home exercise program can reduce the risk of cancer by 61% in people over the age of 70.[5] A 16-week supervised aerobic and resistance exercise intervention appeared to reduce the FRS-predicted 10-year risk of cardiovascular disease in women with early-stage breast cancer with overweight condition or obesity.[6] Preliminary data published over the past decade indicate that exercise following the diagnosis of certain solid tumors may slow disease progression and decrease cancer-related mortality.[7] Nevertheless, more research is needed to understand the relationship between exercise and tumors. Hence, this article aims to offer a detailed overview of the mechanisms behind the antitumor effects of exercise.

2. The effect of exercise on tumor volume, weight and metastasis

Tumor volume, weight, and metastasis are significant parameters that cannot be ignored in the development of tumor and are closely related to the severity of the disease. Tumor burden serves as a biomarker to inform the application of immune checkpoint inhibitors[8]; tumor volume can be used as an indicator of tumor severity. Tumor volume in parathyroid cancer (PC) influences serum levels of parathyroid hormone (PTH), calcium, alkaline phosphatase (ALP), and 25(OH)D, all of which are often linked to PC-related morbidity and mortality[9]; metastasis occurs when

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tumor cells evolve to bypass their natural constraints through interactions with their surroundings. These cells then multiply in a new tissue environment, leading to organ dysfunction and potentially death.[10] Therefore, assessing tumor volume, tumor burden, and the extent of metastasis is essential for gauging the severity of the tumor.

Therefore, we concentrate on the impact of exercise on these factors. In a pancreatic ductal adenocarcinoma model, for instance, Kurz E et al.[11] demonstrated that aerobic exercise reduced 20%–30% tumor weight by modulating systemic and intratumoral immunity. Exercise, in a mechanism that prevents tumor growth, encourages immune mobilization and the accumulation of IL15R $CD8^+$ T cells that infiltrate tumors. Gomes-Santos IL et al.[12] discovered that seven consecutive days of exercise reduced tumor burden in three breast cancer models, with a roughly 30% reduction in tumor weight in the exercise group compared to the control group. In a 4 T1 mouse model of breast cancer, exercise reduced immunosuppression as demonstrated by significantly slower tumor growth in mice in the exercise group compared to sedentary control group.[13] Additionally, decreases in lung weight and surface metastases were observed simultaneously in the exercise group. Table 1 summarizes the impact of exercise on tumor volume, weight, and metastasis, showing that most studies have focused on tumor models such as breast, lung, and prostate cancer. Voluntary wheel running and forced treadmill running were the primary forms of exercise. The studies in this table also support the idea that exercise can decrease tumor volume, weight, and metastasis.

3. The effect of exercise on tumor angiogenesis and its regulatory mechanism

The vasculature of tumors plays a crucial role in the growth and metastasis of solid tumors and should not be neglected when treating them. According to studies,[31] tumor vasculature is highly disorganized, and blood flow is disrupted, impeding the delivery of chemotherapy to cancer cells. For instance, Jain RK et al.[32] discovered that the tumor vasculature was disorganized and leaky, with up to fifty percent of tumor vessels being ineffective. Moreover, Kim SJ et al.[33] demonstrated that tumor vascular leakage and immaturity led to insufficient oxygen and nutrient delivery to the tumor vasculature and promoted cancer cell metastasis to distant organs. This instability of the tumor vasculature also makes it difficult for anti-cancer drugs to penetrate the tumor and reach it.

Numerous studies in the emerging field of exercise oncology have explored how physical activity influences tumor blood vessel formation and its regulatory mechanisms. Schadler KL et al.[31] discovered that increased vascular shear stress induced by aerobic exercise can alter and remodel blood vessels in normal tissues, and data from a mouse model indicate that activation of the calcium-regulated phosphatase-NFAT-TSP1 signaling pathway in endothelial cells plays a crucial role in exercise-induced shear stress-mediated tumor vascular remodeling. Gomes-Santos IL et al.[12] discovered that exercise did not affect vascular density but instead promoted tumor vascular maturation and induced vascular normalization in both the E0771 and MCa-M3C breast cancer models. Exercise increased the proportion of vessels associated with αSMA perivascular cells, an indicator of vascular normalization. Additionally, exercise increased the proportion of vessels that were perfused, indicating improved vascular function. Hypoxia decreased as a result of a more functional vasculature, indicating a normalization of the tumor microenvironment. Table 2 summarizes the literature that supports the conclusion that both forced treadmill running and voluntary wheel running enhance vascular function and promote vascular normalization.

4. The effect of exercise-induced myokines on tumor

Exercise triggers the release of specific humoral factors into the bloodstream and facilitates the transport of signaling molecules generated by muscles to different organs. Myokines, which are cytokines produced by muscles, are secreted into the bloodstream. Research indicates that myokines offer several advantages for cellular metabolism, such as decreasing insulin resistance, enhancing glucose uptake, and reducing obesity. Additionally, the levels of exercise influence the concentration of myokines in the blood. Altered levels of myokines such as IL-6, IL-15, IL-10, irisin, cysteine-rich acidic secretory protein (SPARC), muscle growth inhibitor, tumor suppressor OSM, and nuclear proteoglycan may exert a direct inhibitory effect on cancer growth by inhibiting proliferation, promoting apoptosis, inducing cell cycle arrest and inhibiting hyperthermic transformation to mesenchymal cells.[42] Aoi W et al.[43] demonstrated that exercise stimulates the secretion of SPARC from muscle tissue, which inhibits colon tumorigenesis by increasing apoptosis; Hojman P et al.[44] discovered that post-exercise serum inhibits the proliferation of breast cancer cells and induces apoptosis in these cells, with the myokine OSM possibly mediating this effect. Therefore, the mechanisms underlying the potential protective effects of myokines against cancer merit additional study. Table 3 summarizes additional information regarding the effect of exercise-induced myokines on tumors.

5. The effects of exercise on pH and hypoxia in the tumor microenvironment

Due to anaerobic or aerobic glycolysis, tumor cells thrive in an acidic microenvironment, and lactate production is thought to be a crucial mechanism by which cancer cells evade immune surveillance. By lowering the pH of the microenvironment, lactic acid has been shown[51] to promote cancer cells proliferation, invasion, metastasis, and pathological angiogenesis in tumor tissue. Conversely, aerobic exercise helps to normalize the acidic and immunosuppressed tumor microenvironment. This is evidenced by lower circulating glucose levels, enhanced blood and oxygen delivery to cancerous tissues, reduced glycolysis in both cancer and stromal cells, boosted oxidative phosphorylation, and decreased lactic acid levels through both reduced production and increased clearance.[52] Specifically, endurance exercise downregulated the expression of monocarboxylate transporter protein 1 (MCT 1) and LDH-A as well as increased LDH-B expression in solid tumors and inhibited tumor lactate metabolism, thereby decreasing lactate levels in tumor tissue.[53] Bacurau RF et al.[54] discovered that treadmill exercise decreased the peripheral conversion of glucose to lactate in macrophages and lymphocytes by approximately 50% in rats with holo sarcoma.

Hypoxia plays a crucial role in the tumor microenvironment, significantly influencing cell growth, the formation of new blood vessels, metabolism, and the immune response. It can also accelerate tumor progression, enhance aggressiveness, boost metastatic potential, and lead to a poor prognosis.[55] According to studies,[56] abnormal vascular architecture induces increased glycolysis in tumor cells and a subset of stromal cells, thereby producing a hypoxic tumor microenvironment with elevated lactate levels. Buss LA et al.[57] noticed that voluntary wheel running slowed the development of primary and secondary breast tumors and decreased hypoxia in tumors. However, in another study,[40] researchers observed that in the B16-F10 melanoma model and the EO771 mammary tumor model, exercise after tumor implantation did not significantly alter the area of hypoxia or the number of perfused vessels in the exercise group compared to non-exercised mice. The varied physiological impacts of exercise indicate that future preclinical research should focus on integrating exercise into standard cancer therapies. Betof AS et al. found[21] that in a mouse model of 4T1 mammary tumor, tumor hypoxia was significantly lower in freely running mice compared to controls, and demonstrated that it was due to aerobic exercise stimulating ‘productive’ or ‘physiological’ angiogenesis and vascular normalization, resulting in a significant reduction in intra-tumor hypoxia. In a clinical in situ model of prostate cancer in rats, treadmill exercise improved tumor perfusion and decreased hypoxia, in part due to reducing vasoconstriction.[35]

Table 1
The effect of exercise on tumor volume, weight and metastasis.

Tumor type	Exercise modality	Exercise modes/types and intensity	Tumor progress results	Tumor metastasis	Reference
Pancreatic cancer/ orthotopically implanted mutant $p53^{R172H/+}$; $KRAS^{G12D/+}$; $pdx\text{-}1^{Cre/+}$ (KPC) cells	Forced treadmill running	aerobic exercise; 5 times/week, 30 min/d, 15 cm/s	Exercise ↓ 20%–30% tumor weight		11
Mammary/E0771, EMT6, MMTV-PyMT, MCa-M3C BC cells, injected orthotopically	Forced treadmill running	aerobic exercise; at ~60% of maximal velocity	Seven days of consecutive exercise ↓ tumor burden in the three models of BC		12
Mammary/subcutaneously inoculated with 5×10^4 4T1 cells	Forced treadmill running	aerobic exercise; a duration of 30 min per day (speed = 18 m/min)	Tumor growth and tumor volume was ↓ in the exercise group compared to control group	A non-significant reduction in lung weight and number of surface metastases were also observed in the exercise group	13
Mammary/1×10^6 MAD-MA-231 cells injected orthotopically	Voluntary wheel running	aerobic exercise; a wheel measuring 11.5 cm in diameter	No change in primary tumor growth; Exercise significantly increased intratumoral perfusion/ vascularization and hypoxia relative to sedentary control counterparts		14
Lung/2.5×10^5/50 μL/mouse Lweis lung carcinoma cells s.c.	Voluntary wheel running	aerobic exercise; an average of 4–6 km/d for the duration of the experiment	No difference in tumor cross-sectional area and tumor volume	Trend to inverse relationship between running distance and metastatic tumor yield	15
Mammary/Transgenic	Forced treadmill running	aerobic exercise; 60 min/d (20 m/min and 5% grade), 6 d/week for a period of 20 weeks	Exercise ↓ tumor volume at 21 and 22w		16
Prostate/5×10^5 mouse prostate C-1 cells, orthotopically	Voluntary wheel running	aerobic exercise; voluntary access to a wheel 24 h/d for the duration of the study	Primary tumor growth was comparable between groups	EX ↓ tumor nodal involvement by 36%, metastases weight by 88% and number of metastases by 34%	17
Prostate/surgical s.c. Implantation of R3327 Dunning AT1 tumor fragment	Forced treadmill running	aerobic exercise; 5 d/week; One week 15 min at 20 m/ min; 2 weeks 40 min at 22 m/min; 2 weeks 60 min at 25 m/min.	Exercise rats had smaller tumors at 14 and 21 days compared to SED controls		18
Mammary/1×10^4 cells in 4th mammary fat pad	Voluntary wheel running	aerobic exercise; Running wheels (measuring 15.5 cm by diameter)	Inverse relationship between distance run and final tumor mass		19
Lung cancer/Luciferase-tagged A549 lung adenocarcinoma cells were injected through the tail vein	Voluntary wheel running	aerobic exercise; cages with running wheels present	Lung tumors in exercising mice grew significantly more slowly relative to sedentary mice	There was no change in the development of metastatic lesions between the two groups	20
Mammary/5×10^5 4T1-luc or 2.5×10^5 E0771 cells in dorsal mammary fat pad	Voluntary wheel running	aerobic exercise; continuous access to an 11.5 cm diameter wheel	Exercise slowed tumor growth compared to SED		21
B16F10 melanoma	Voluntary wheel running	aerobic exercise; voluntary running	Wheel running reduced tumor growth by 61% and similar reductions in tumor volume of 67% and 53% in female adult and old mice	Wheel running dramatically ↓ lung metastases	22
Liver cancer/injected with 5×10^6 Hepa1-6 cells subcutaneously and by tail vein 3×10^6 Hepa1-6-GFP cells	Swimming	aerobic exercise; regular moderate swimming (8 min/d, 9 weeks); overload swimming (16 and 32 min/d, 9 weeks)	Regular moderate swimming suppressed growth, and prolonged survival while overload swimming had the opposite effect	Regular moderate swimming reduced lung metastasis	23
Breast cancer/MC4L2 cancer cells were injected	Forced treadmill running	progressive aerobic training for 6 weeks; gradually increasing speeds10, 12, 14, 18 m/min, 5 d/week	Exercise ↓ growth rate and final weight of the tumor		24
Walker 256 tumor-bearing rats	Forced treadmill running	aerobic exercise; 8 weeks, 3 d/week, 44 min/d, at 55%–65% VO_2 max	Exercise showed significant reductions in tumor growth, cachexia and carcass weight compared to the sedentary rats	Metastasis ↓	25
Mammary/4 T1 cells were injected subcutaneously into the 4th mammary pad at the end of the training period	Forced running wheels	endurance training, aerobic exercise; 5 d/week, for 8 consecutive weeks	Exercised wild-type had 17% slower growth rate, 24% longer survival, and 2-fold tumor-CD 8/FoxP3 ratio than sedentary controls		26
Mammary/subcutaneous injection with a murine mammary cancer line, the I3TC cell line	Voluntary wheel running	aerobic exercise; an initial 10 min warm-up (10 m/min) was followed by gradual increases of 2 m/min every 2 min	Exercise significantly ↓ tumor growth and ↑ survival times relative to animals not given access to an exercise wheel		27
Glioma/40,000 GL261 cells were injected	Voluntary wheel running	aerobic exercise; voluntary physical exercise	Exercise ↓ cell proliferation; not find any differences in the tumor sizes of the running group relative to the sedentary mice		28
Melanoma/a murine Ret-melanoma cell line derived from a spontaneous	Forced treadmill running	aerobic exercise; 20 min followed by 8 cm/s for 5 min, increasing the speed at 2 cm/s until 24 cm/s and then sustained for 8 min, the	Exercise ↓ primary melanoma volume	Exercise ↓ metastatic dissemination into lymph nodes, lungs, and liver	29

(*continued on next page*)

Table 1 (*continued*)

Tumor type	Exercise modality	Exercise modes/types and intensity	Tumor progress results	Tumor metastasis	Reference
melanoma in Ret-transgenic mice		speed was gradually decreased by 2 cm/s every minute until 18 cm/s			
Colon carcinoma/1 × 10^5 CT-26 cells were injected subcutaneously into the right flank area of the mice	Swimming	aerobic exercise; physical training in water (30 ± 2 °C) twice per day for 30 min intervals	Swimming obviously ↓ tumor volume and weight		30

Table 2
The effect of exercise on tumor angiogenesis and its regulatory mechanism.

Tumor type	Exercise modality	Exercise modes/types and intensity	Tumor angiogenesis	Regulation mechanism	Reference
Mammary/syngeneic 4T1 murine breast cancer cells orthotopically in the dorsal mammary fat pad	Voluntary wheel running	aerobic exercise; continuous access to an 11.5 cm diameter wheel	Tumor vessel density, function and maturity ↑	Expression of VEGF ↑, PDGFR-β ↓	21
Dunning R-3327 AT-1 tumor cells (10^4) were injected into the ventral prostate	Forced treadmill running	endurance aerobic exercise; treadmill running 5 d/week for 60 min/d at 15 m/min	Tumor microvascular PO2 ↑ ~100%		34
Prostate cancer/The Dunning R3327-MatLyLu (MLL) rat prostate carcinoma cell line	Forced treadmill running	aerobic exercise; walked for 5 min/d for 5 days at a 10° incline and a speed of 15 m/min	Mean arterial pressure, soleus muscle blood flow, and prostate tumor blood flow ↑	In part to a diminished vasoconstriction	35
Breast cancer/MC4-L2 cells were inoculated in the right inguinal flank near to back of the animals	Forced treadmill running	interval exercise; 16–18 m/min, 0 grade, 10–14 min, 5 d/week for 5 weeks	Tumor angiogenesis ↓	miR-21, miR-206, and let-7a pathways may involve the anti-angiogenesis effects of interval exercise training with hormone therapy in mice breast tumors.	36
Mammary/a single intraperitoneal administration of the carcinogen agent MNU	Forced treadmill running	long-term exercise training; 60 min/d, 5 times/week during 35 weeks	Tumor vascularization ↑	VEGF-A immune expression ↑	37
Ewing sarcoma/A637 tumor cells (2.5 × 10^6) and TC cells (2 × 10^6) were injected subcutaneously into the backs of mice.	Forced treadmill running	moderate intensity (60–70% VO_2 max) treadmill running; 12 m/min for 45 min for 5 consecutive days per week for 2 weeks	Exercise does not significantly alter vessel morphology (open lumens, total vessels, microvessel densities, or numbers of elongated vessels); Exercise ↓ tumor vessel hyperpermeability.		38
Mice bearing subcutaneous pancreatic ductal adenocarcinoma-derived PDX tumors	Forced treadmill running	moderate treadmill running; 5 d/week for 2 weeks	Tumors from exercised mice had more vascularity than tumors from control mice did.		39
1×10^6 B16-F10 cells in 50 μL sterile PBS subcutaneously into the shaved right flank; 2×10^5 EO771 cells in 20 μL sterile PBS into the 4th mammary fat pad.	Running wheel	voluntary physical exercise; 17 days for mice bearing melanomas and 21 days for mice bearing breast tumors	Exercise does not change CD31 vessel density in B16-F10 or EO771 tumors.		40
Breast cancer/subcutaneous injection of MC4-L2 cancer cells	Forced treadmill running	aerobic exercise; 8 weeks and 5 sessions per week of running with an intensity of 14–20 m/min	Exercise ↓ angiogenesis and ↑ apoptosis activity in the breast tumor tissue		41

6. The effect of exercise on antitumor immunity

6.1. Innate immunity

The relationship between immune disorders and tumors is complex and multifaceted. The immune system plays a crucial role in both the prevention and treatment of tumors, while tumor cells continuously evolve to evade immune surveillance. A deeper understanding of this relationship is essential for developing new anticancer strategies and therapeutic approaches.

Tumors are collections of malignant cells and complex, well-organized ecosystems. The immune component within the tumor, referred to as the tumor immune microenvironment (TIME), has been associated with tumor development, recurrence, and metastasis.[58] The TIME is a complex ecosystem of adaptive and innate immune cells with anti-tumor effects.

Natural Killer (NK) cells are an essential component of innate immunity, and exercise influences their number and function. NK cells comprise 5–15 percent of all circulating lymphocytes in healthy adults.[59] Activated NK cells have the primary function of killing infected (e.g., viral) or transformed (malignant) cells and inducing adaptive immune responses via the release of cytokines. The exercise-induced mobilization of NK cells is a very rapid phenomenon. Seventy seconds of stair climbing can increase the number of NK cells in the blood by a factor of six.[60] One study found that NK cell infiltration was significantly higher in the tumors of mice that were exercising, whereas NK cell depletion promoted tumor growth and diminished the beneficial effects of exercise.[22] Analysis of the underlying mechanisms suggests that adrenaline mobilizes NK

Table 3
The effect of exercise-induced muscle factors on tumor.

Tumor type	Exercise modality	Exercise modes/types and intensity	Changes or Treatment	Regulation mechanism or outcome	Reference
Pancreatic cancer	Forced treadmill running	aerobic exercise; 5 times/week, 30 min/d, 15 cm/s	Serum IL-15 ↑	Immune mobilization and accumulation of tumor-infiltrating IL15Rα+ CD8 T cells	11
Melanoma, Lung cancer	Voluntary wheel running	aerobic exercise; voluntary running	Serum IL-6 ↑	NK cell mobilization and redistribution ↑	22
Breast cancer	Endurance exercise on a treadmill	endurance exercise; 5 days per week for 8 weeks	IL-6 ↓ VEGF ↓ tumor volume ↓	Decreased IL-6 production could reduce the generation of VEGF, resulting in reduced intra-tumor angiogenesis.	45
Colon carcinogenesis	Swimming	aerobic exercise; from 20 (first week) to 60 min (third week), a training period kept steady for the next 5 weeks	IL-10 levels ↑		46
Colon cancer	High-intensity intermittent training	high-intensity intermittent swimming training; (twelve 20-s swimming with a weight (16% body weight) with 10-s pauses between the bouts, 5 d/week for 4 weeks	Rat: SPARC ↑ in epitrochlearis muscle and serum Human: Protein levels of SPARC in serum ↑; mRNA of SPARC in vastus lateralis muscle ↑	ACF ↓	47
4 T1 mammary carcinoma	Aerobic interval training on a treadmill	aerobic interval training; 6 m/min, increased 3 m/min, every 3 min until exhaustion	Oncostatin-M and tumor necrosis factor-α levels in tumor tissue ↑	Exercise and antioxidants such as selenium affect both antitumor immune responses and tumor cytokine expression.	48
Colon cancer	Acute aerobic exercise	moderate-intensity aerobic interval exercise; 6 × 5 min intervals at 60% heart rate reserve	Serum IL-6 ↑	May be driven by IL-6-induced regulation of DNA damage and repair.	49
Prostate cancer	Supervised resistance training, self-directed aerobic exercise	12-week supervised resistance training, self-directed aerobic exercise, and protein supplementation	Serum OSM levels and relative serum OSM levels ↑	Tumor-suppressive effects	50

cells and blocking-adrenergic signaling inhibits exercise-dependent tumor suppression. Pal A et al.[61] found that acute and chronic endurance training modulates NK cell function via the AhR/IDO axis. The study examined the effects of acute exercise and various chronic endurance exercise programs on the levels of AhR (Aryl hydrocarbon receptor) and IDO (Indolamine 2,3–dioxegenase), as well as the activating (NKG2D) and inhibiting (KIR2DL1) receptors on NK cells. Promising cancer therapies based on interventions in the AhR/IDO axis are already being studied extensively. Additionally, there are studies that summarize the most current findings regarding the functions of AhR and IDO in immune cells, particularly in relation to the pathogenesis of autoimmune diseases in response to various stimuli. And Anna et al. identified multiple myeloma inhibition through inhibition of the aryl hydrocarbon receptor/polyamine biosynthesis axis.[62] These studies are clinically relevant as exercise is a key player in immune regulation.

Other cells in the innate immune response are also involved in the anti-cancer effects of exercise, with macrophages, particularly tumor-associated macrophage (TAM), playing a significant role in anti-cancer immunity. The pro-inflammatory M1 phenotype exerts anti-cancer effects by releasing factors such as interleukin 10 (IL-10), transforming growth factor beta (TGF-β), and glucocorticoids. In contrast, the anti-inflammatory M2 phenotype exerts tumor-promoting effects. According to research, exercise can exert anti-cancer effects by altering the polarization of macrophages. Kim MK et al.[63] revealed that exercise decreased M2 macrophage polarization in breast tumor tissue, strongly associated with tumor growth. The myokine, myostatin, reduced M2 macrophage polarization through the inhibition of the JAK-STAT signaling pathway. As suggested by these results, continuous low-intensity exercise may delay breast cancer development and growth and reduce tumor volume by inducing apoptosis and inhibiting M2 macrophage polarization. Kawanishi N et al.[64] explored the impact of exercise training on the phenotypic shift of macrophages in the adipose tissue of high-fat-induced obese mice. They discovered that exercise training might induce the phenotypic switching from M1 macrophage to M2 macrophage in obese adipose tissue besides inhibiting M1 macrophage infiltration into adipose tissue. In tumors of sedentary mice,[65] cytokine synthesis of M1 macrophages is reduced, and the presence of M2 macrophages is increased, whereas physical activity reduces tumor development and polarizes the immune response toward anti-tumor M1 in the fact of tumors.

There are pro-tumor N2 and anti-tumor N1 subtypes of tumor-associated neutrophils (TAN). By regulating cancer cell survival and migration, immune function, and angiogenesis, it is widely accepted that N2 TAN, directly and indirectly, contributes to cancer progression and metastasis.[66] Swimming was associated with reduced macrophage infiltration and neutrophil accumulation, delaying mouse tumor development.[67] In addition, it has been demonstrated[68] that prolonged, vigorous daily exercise delays tumor growth, decreases the number of inflammatory cells (macrophages and neutrophils), and reduces the probability of blood vessels within the tumor. Myeloid-derived suppressor cells (MDSCs) consist of immature monocytes (M-MDSCs) and granulocytes (PMN-MDSCs), which can inhibit adaptive immunity and impede the efficacy of cancer therapy.[69] Immunosuppression is an essential feature of MDSCs. Although MDSCs are associated with inhibiting multiple immune cells, their primary target is T cell.[70] In a mouse model of pancreatic cancer, researchers have found that exercise decreased MDSCs and partially reversed their T-cell-suppressing activity.[11]

6.2. *Adaptive immunity*

Exercise influences adaptive anti-cancer immunity as well. T lymphocytes of the adaptive immune system are crucial for tumor immunity, and these T cells are generated by cross-stimulation against tumor-associated antigens.[71] Kurz E et al. found in a mouse model of pancreatic ductal adenocarcinoma[11] that exercise promoted immune mobilization and accumulation of tumor-infiltrating IL15Rα CD8 T cells, which acted as tumor protectors. Another study[12] encountered that in a mouse model of breast cancer, exercise training improved tumor control by increasing $CD8^+$ T cell infiltration via CXCR3 signaling and sensitizing breast cancer to immune checkpoint inhibition. In mice, exercise-induced reductions in tumor growth were dependent on $CD8^+$ T cells, and metabolites produced in skeletal muscle were secreted into plasma at high levels during exercise in both mice and humans, enhancing the effects of $CD8^+$ T cells, indicating that $CD8^+$ T cells are altered, and their anti-tumor efficacy is enhanced by exercise metabolism.[27] Inhibiting the

recruitment of Treg cells to cancer, endurance exercise has been shown to slow the growth of mammary tumors in mice.[26] The stimulating effect of exercise on $CD8^+$ T cells may enhance the efficacy of standard cancer therapies such as immunotherapy and radiotherapy.

7. The effect of exercise on cancer chemotherapy

Chemotherapy, which uses drugs to kill cancer cells, is one of the most effective ways of treating cancer. However, chemotherapy can produce general side effects. For example, various chemotherapies are used to treat testicular tumors and can produce general side effects such as anaemia, neutropenia, nausea, vomiting, diarrhoea, mucositis or parvovasculitis, as well as specific toxicities such as ototoxicity, nephrotoxicity, pneumatotoxicity, neurotoxicity, or Raynaud's syndrome.[72] Opioids are very useful medications to reduce suffering of cancer patients such as refractory pain and dyspnea, it also have some side effects of constipation, nausea and vomiting, respiratory depression.[73] Regular physical activity helps to reduce complications associated with treatment, such as fatigue. A growing body of research suggests that exercise may increase the effectiveness of chemotherapy in fighting tumors. Table 4 summarizes studies that have looked at the role of exercise in improving the effectiveness of chemotherapy for cancer.

8. Difference of exercise prescription

Clinical and preclinical studies have shown that whether exercise has an anti-tumor or pro-tumor effect depends on the context, including tumor type and exercise parameters. In most cases, exercise can reduce the incidence of a wide range of cancers. In patients diagnosed with cancer, activity can also inhibit cancer progression, reduce cancer symptoms and side effects of cancer therapy, enhance patient tolerance of treatment, and lengthen patient survival.[79] Nonetheless, it has been discovered[80] that exposure to forced treadmill exercise of varying intensities accelerates tumor growth relative to sedentary controls. Therefore, the choice of prescribed exercise is also crucial. Exercise regimens investigated in preclinical studies should be replicated as closely as possible in human studies evaluating exercise regimen parameters. Some key parameters include[81]: modality/paradigm (forced versus voluntary); dose (intensity, duration of exercise, number of sessions per week, and duration of treatment) and timing (time to start exercise).

Different effects may result from variations in exercise prescription parameters. In some clinical studies, for instance, for women undergoing hormone therapy for breast cancer, Pilates was more effective than circuit training in reducing arthralgia.[82] The performance of stretching, strengthening, and aerobic exercises for 40 min, five times a week for four weeks, has been found to improve physical function, reduce fatigue, and increase muscular strength in patients with unilateral lower-limb lymphedema after gynecologic cancer surgery.[83] Patients with advanced gastrointestinal cancers show good compliance with resistance and aerobic exercise during palliative chemotherapy for 6 weeks.[84] The results of this secondary analysis of the Women's Activity and Lifestyle Study in Connecticut trial suggest that a 6-month aerobic exercise intervention, compared to attention control, led to a significant improvement in self-reported Chemotherapy-induced peripheral neuropathy among patients who had undergone treatment for ovarian cancer.[85] According to the findings of Do JH et al., upper body resistance exercise has shown to have a beneficial impact on arm function and

Table 4
The effect of exercise on cancer chemotherapy.

Tumor type	Exercise modality + chemotherapeutic drug	Outcome	Potential regulation mechanism	Reference
BALB/c female mice with syngeneic 4T1 murine breast cancer	voluntary wheel running (high-intensity, short-duration exercise) + cyclophosphamide IP (100 mg/kg)	Exercise significantly reduced the delayed tumor growth effect of the chemotherapy drug cyclophosphamide.	Exercise may normalize the tumor vasculature, reduce tumor hypoxia and increase tumor sensitivity to chemotherapy.	21
Pancreatic tumor	moderate treadmill exercise (12 m/min, 45 min/day, 5 d/week) + gemcitabine (15 mg/kg)	The time to tumor regression was significantly shorter in mice receiving the combination of exercise plus gemcitabine than in mice receiving gemcitabine alone.	Exercise causes changes in the structure and function of the tumor vasculature, improving the delivery and efficacy of chemotherapy.	39
Ewing sarcoma	treadmill running (moderate intensity (60%–70% VO_2 max) treadmill running at 12 m/min for 45 min for 5 consecutive days per week for 2 weeks) + doxorubicin (2.5 mg/kg)	Tumors from mice treated with the combination of exercise and doxorubicin were significantly smaller than tumors from mice treated with doxorubicin (DOX) alone in both the A673 and TC71 models.	Exercise reduces hypoxia, increases DOX delivery.	38
MDA-MB-231 Breast Cancer Xenografts	Exercise (18 m/min at 0 grade for 45 min, 5 d/week for 8 weeks) + doxorubicin (4 mg/kg)	No significant difference between the DOX-only and exercise + DOX groups.		74
B16F10 melanoma and pancreatic ductal adenocarcinoma	treadmill running (45 min of treadmill running for 5 consecutive days per week at 12 m/min) + doxorubicin (2 mg/kg) or gemcitabine (3 times per week)	Adding aerobic exercise to chemotherapy inhibited tumor growth in both B16F10 and PDAC-4662 tumors significantly more than chemotherapy alone.	Increased blood flow due to aerobic exercise triggered the remodeling of tumor vessels to a more functional state.	31
B16F10 melanoma	treadmill walking (10 m/min, 45 min/day, 5 d/week, 2 weeks) + doxorubicin (4 mg/kg)	Exercise increases the efficacy of DOX in inhibiting tumor growth without mitigating subclinical DOX-induced cardiotoxicity in a murine model of melanoma.	DOX and exercise alter the mTOR pathway.	75
Mammary carcinoma	aerobic rotarod exercise and resistance training (10 min/sessions, 2 min rest between sessions/5 days) + doxorubicin (5 mg/kg)	DOX + Exercise group had a significantly lower tumor volume and weight than the Dox group.	Physical training enhances the efficacy of DOX in treating breast cancer by activating cytotoxic immune cells, releasing tumor suppressor factors, and initiating mt-apoptosis, while also mitigating the adverse effects of chemotherapy.	76
Breast cancer	supervised resistance or aerobic exercise (beginning 1–2 weeks after starting chemotherapy and ending 3 weeks, during chemotherapy	The exercise regimen resulted in improved self-esteem, physical fitness, body composition, and chemotherapy completion rate.		77
Colon Cancer	supervised exercise (a warming up, aerobic and muscle strength training, and a cooling down) during chemotherapy	The intervention significantly reduced physical fatigue.		78

muscular strength in individuals with breast cancer related lymphedema. Importantly, this effect was observed without any increase in arm volume, even during and shortly after intensive CDT lymphedema treatment.[86] However, a study suggested that sixteen weeks of 150 min of moderate-intensity aerobic exercise per week did not appear to significantly improve physical function in women with advanced breast cancer.[87] Table 5 summarizes the results of exercise in clinical trials.

In two distinct preclinical models of prostate cancer, Dufresne S. et al.[96] compared the effects of running on a treadmill versus running on a voluntary wheel. They found that only treadmill running slowed the growth of tumors. Almeida and colleagues[67] observed that when experiments were conducted at two swimming intensities of 50% or 80% of maximum load, 50% intensity significantly inhibited tumor growth, while 80 percent intensity had no effect. In a female mouse B16F10 melanoma model, four weeks of voluntary wheel running prior to tumor cell vaccination reduced tumor growth by 61%; however, in the slow-growing DEN-induced and TG(GRM1) EPV tumor models, beginning running after tumor formation was sufficient to control tumor incidence and progression.[22]

In general, most terminal cancer patients are physically and mentally exhausted due to severe pathological symptoms and the side effects of medication. Their bodies are no longer able to function at full capacity. Under such circumstances, engaging in any kind of physical activity or exercise may aggravate their condition, potentially worsening their situation. For example, patients with upper limb and shoulder problems after breast cancer treatment should seek medical advice before participating in upper body exercises. Patients with colorectal cancer fistulas need medical clearance to participate in contact sports and avoid weight-bearing exercises. Patients with gynaecological tumors with swelling or inflammation of the abdomen, groin or lower limbs should seek medical advice before participating in lower body exercises. Patients with bone metastases with pathological fractures and spinal cord compression are not suitable for exercise. Contraindications to exercise in patients with multiple myeloma include untreated hypercalcaemia, myelodysplasia, renal insufficiency.[97] Therefore, exercise for oncology patients is not aimed at muscle gain and fat loss, but at improving the physical and psychological condition of patients to help everyone to have a better treatment, recovery and quality of life. Studies have shown that exercise intervention can accelerate the recovery of patients' postoperative functions, improve the symptoms of cancer-related fatigue caused by radiotherapy and chemotherapy, and to some extent improve the prognosis of malignant tumor survivors and reduce the risk of death.[98] Cancer survivors can safely exercise to improve cardiovascular fitness, build muscle strength, improve quality of life, reduce fatigue and alleviate depression.[99,100]

Exercise is a fundamental strategy for maintaining and restoring balance in the body at various levels, including organismal, tissue, cellular, and molecular. It can also prevent or mitigate numerous diseases, such as cancer. Aerobic exercise, also known as endurance exercise, consists of rhythmic activities performed over an extended period while ensuring sufficient oxygen supply. This form of exercise utilizes glucose, fats, and proteins as fuel, offering a steady but prolonged energy supply that enhances the performance of the heart, lungs, and circulatory system. Resistance exercise, or strength training, involves quick muscle contractions over short periods, often without enough oxygen. This enables high-speed, intense workouts. The main energy source for anaerobic metabolism in this exercise is glucose, which provides quick but short-lived energy. Resistance exercise specifically strengthens trunk and limb muscles. Wheel running represents a general form of physical activity, while treadmill running is more structured and intentional. Cancer is a genetic disorder caused by multiple factors over time. Exposure to environmental carcinogens—such as chemicals, physical agents, and viruses—along with genetic predispositions, hormonal, gender, and age-related factors, can lead to genetic mutations, resulting in malignant tumors. Due to the great heterogeneity of the various tumors, different intensities of exercise result in significantly different alterations to mammalian physiology and gene expression[101] and have distinct effects on tumor outcomes. Similarly, the timing of interventions regarding exercise therapy for cancer patients also deserves some thought. Selecting the appropriate exercise regimen is complex and requires further research. Exercise tolerance in cancer survivors is often inadequately assessed, underscoring the necessity to customize exercise programs for each individual. This customization should be conducted under close supervision, considering both relative and absolute contraindications. It is recommended to start with low-intensity exercise, gradually increasing to moderate and then high intensity, while simultaneously extending the duration of the sessions. Due to the diverse nature of tumors, exercise prescriptions should be tailored to different tumor types and patient conditions. Individual differences must be considered when determining the type, intensity, duration, and timing of exercise.

Table 5
The results of exercise in clinical trials.

Tumor type	Exercise interventions	Results	Reference
Breast cancer	stretching, strengthening, physical activity, and behavioral change techniques to support adherence to exercise	It has good clinical efficacy and cost-effectiveness, and can reduce the disability of upper limbs after one year of treatment in patients at high risk of complications after breast cancer surgery.	88
Breast cancer	moderate-vigorous (65%–85% heart rate maximum) aerobic and resistance exercise thrice weekly for 16 weeks	Good improvements were made in quality of life, fatigue, depression, estimated maximum oxygen saturation, muscle strength, osteocalcin, and BSAP.	89
Breast cancer	supervised and group-based resistance exercise, 2/week over 12 weeks	Physical fatigue ↓ and maintain QoL during chemotherapy.	90
Prostate cancer	20 weeks of resistance exercise training with supplementation of 31 g whey protein, consumed immediately after exercise and every night before sleep	Resistance exercise training counteracts the adverse effects of ADT on body composition, muscle mass, muscle strength, and aerobic capacity.	91
Head and neck cancer	a structured exercise program of aerobic and active resistance exercises for a period of 11 weeks	It improves their function and quality of life and prevents fatigue from worsening.	92
Prostate Cancer	12 weeks of thrice-weekly, supervised aerobic sessions on a treadmill at 85%–95% of peak oxygen consumption	Cardiorespiratory fitness levels ↑, prostate-specific antigen levels ↓, PSA velocity ↓, and prostate cancer cell growth ↓	93
Breast cancer	Supervised, progressive, moderate to vigorous aerobic and resistance exercise 3 times per week for 16-week	Shoulder active range of motion ↑, upper extremity isometric strength ↑, and disabilities of the arm, shoulder, and hand and Penn Shoulder Scale scores ↑	94
Metastatic castrate-resistant prostate cancer	Supervised multimodal aerobic and resistance	No significant change in body composition was observed. Adjusted serum OSM and relative OSM, serum SPARC and relative SPARC ↑	95

9. Conclusions and future perspectives

Exercise suppresses tumors by influencing various biological processes throughout the body, including circulating substances, signaling pathways, immune regulation, and metabolism. Further research is needed into exercise prescriptions for cancer patients, particularly those with advanced cancer who may face complex issues and increased risks from exercise. Developing a standardized method for quantifying exercise prescriptions in oncology will enable comparisons across studies. Whether the exercise is aerobic, resistance, mind-body, or a combination, understanding the mechanisms through which it affects tumors is essential. Most clinical protocols currently use exercise as an adjunct to surgery, radiotherapy, chemotherapy, or immunotherapy, rather than as a standalone therapy. To inform clinical trial design and clarify the mechanisms behind exercise-induced changes in tumor outcomes, it is important to evaluate the interactions between exercise and conventional or novel immunotherapies and pharmacodynamics in future preclinical studies.

Ethical Approval

Not applicable.

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Conflicts of interest

The authors declare no conflicts of interest.

CRediT authorship contribution statement

Zhongyu Wang: Writing – original draft, Conceptualization. **Zongming Wang:** Writing – original draft, Conceptualization. **Huitong Chen:** Data curation. **Siyuan Li:** Data curation. **Junhua Yang:** Visualization, Supervision. **Yuxin Ma:** Visualization, Supervision. **Chang Zhou:** Visualization, Supervision. **Xiaobao Jin:** Visualization, Supervision. **Jing Liu:** Writing – review & editing, Project administration. **Xin Wang:** Writing – review & editing, Funding acquisition.

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