



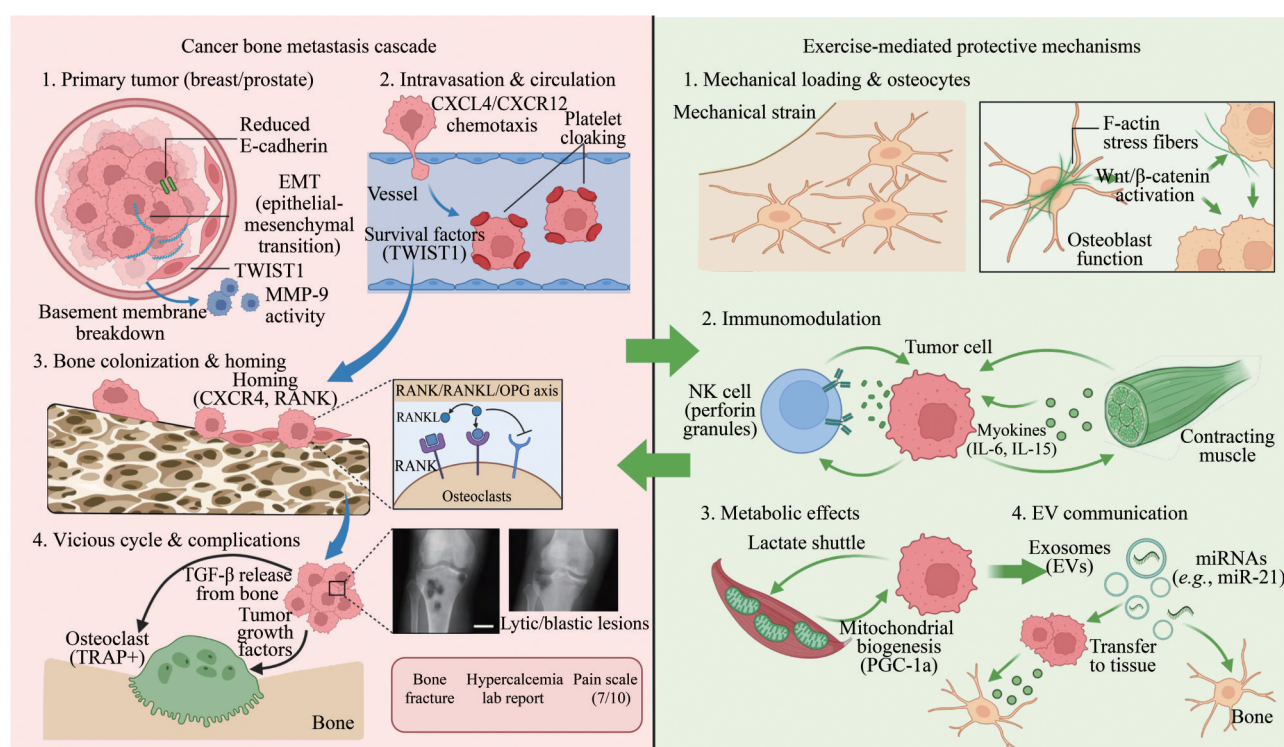
Mechanisms of Exercise Intervention in Cancer Bone Metastasis*

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Graphical abstract



Abstract Bone metastases are a common and serious complication of solid tumors such as breast cancer, prostate cancer, lung cancer, and kidney cancer, and occur at a high rate in patients with advanced cancer. This pathological process not only frequently leads to skeletal-related events such as severe bone pain, pathological fractures, spinal cord compression, and hypercalcemia—conditions that severely impact patients' quality of life—but may also significantly increase the risk of death. Cancer bone metastasis is a complex, multistage cascade involving key steps such as the detachment of tumor cells from the primary tumor, their invasion and entry into the bloodstream, and their colonization, dormancy, and reactivation within the bone microenvironment. In

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recent years, exercise—as a safe and easily implementable non-pharmacological intervention—has demonstrated significant potential in inhibiting bone metastasis, improving the bone microenvironment, and alleviating related clinical symptoms. Its mechanisms of action may involve multiple levels. First, at the mechanical load level, mechanical signals generated by exercise can directly act on bone cells, inhibiting tumor cell infiltration and colonization by regulating endothelial cell permeability and osteoclast activity. Second, at the endocrine and paracrine levels, exercise can alter the expression profiles of microRNAs (such as *miR-486* and *miR-34b*) carried by extracellular vesicles and particles (EVPs) in the circulation, thereby inhibiting tumor cell proliferation and migration by targeting cell cycle-related genes. Furthermore, exercise can remodel the immune microenvironment, enhance the cytotoxic activity of antitumor immune cells, and improve oxygen supply to tumor tissues, thereby alleviating hypoxia-induced immunosuppression. Finally, at the metabolic intervention level, exercise can induce systemic metabolic reprogramming, increasing the nutritional demands of normal tissues, thereby competing with tumor cells for nutrients and forming a “metabolic barrier” in distal organs such as bones. This article reviews the pathogenesis and classification of bone metastases, including osteolytic, osteogenic, and mixed types, and elaborates in detail on the complex processes by which tumor cells undergo colonization, dormancy, and reactivation within the bone microenvironment. Furthermore, based on a comprehensive analysis of human and animal studies on exercise interventions for bone metastases, this paper highlights the mechanisms by which exercise inhibits tumor formation, growth, and spread through the regulation of mechanical loading, extracellular vesicles and granules, as well as *via* immune and metabolic pathways, thereby interfering with bone metastasis. However, the array of exercise modalities and intensities available for patients grappling with the challenges of cancer-related bone metastases remains markedly constrained, and the formulation of tailored exercise prescriptions continues to be devoid of robust, evidence-based medical backing. This review aims to explore the effects of exercise on bone health in patients with bone metastases, analyze the factors and considerations that should be taken into account in exercise prescriptions, and provide new theoretical support and insights for developing personalized exercise programs for these patients and further advancing relevant clinical research. Future research directions should include the development of evidence-based, personalized exercise prescriptions and further clarification of the safety boundaries and best practice standards for exercise interventions, thereby promoting the advancement of relevant clinical research and ultimately improving patients’ clinical outcomes and quality of life.

Key words cancer, bone metastasis, exercise, tumor

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According to global cancer statistics, approximately 10 million deaths in 2022 were attributable to cancer and its related complications, accounting for roughly one-sixth of all global deaths. This makes cancer one of the leading causes of mortality worldwide^[1]. Approximately 118 million new cancer cases are diagnosed each year, and around 50% of patients progress to metastatic disease^[2]. Bone tissue is among the most common sites for metastatic tumor growth. Regions such as the spine, pelvis, skull, ribs, and the proximal humerus and femur have a rich red bone marrow distribution, making them particularly susceptible to tumor cell invasion^[3]. This pattern is especially pronounced in malignancies such as breast cancer, prostate cancer, and lung cancer. Research indicates that modifying lifestyle and environmental risk factors can significantly reduce adverse outcomes in cancer patients^[4]. Regular exercise is associated with lower cancer incidence^[5], recurrence rates^[6], and mortality^[7]. Epidemiological data indicate that regular exercise reduces the risk of at least 13 distinct types of cancer^[8]. Through

mechanisms such as improving the tumor microenvironment, inhibiting cancer progression, and mitigating treatment side effects, exercise significantly enhances patient survival rates and quality of life. This effect is particularly pronounced in breast and prostate cancers. Furthermore, exercise effectively reduces the risk of recurrence in these cancers. Concurrently, preclinical data indicate that various exercise interventions, including voluntary running wheels, treadmill running, and swimming, can significantly reduce tumor incidence, growth, and metastasis in rodent models of multiple cancers, including both genetically and chemically induced tumors^[9-10].

In recent years, exercise has gained increasing recognition as a safe and readily implementable non-pharmacological intervention for managing cancer-related complications. Its effects on bone metastasis in cancer and the underlying regulatory mechanisms have become a focus of research. Accordingly, this paper systematically reviews the complex, multi-stage process of cancer bone metastasis, including the

detachment and invasion of tumor cells from the primary tumor, intravascular infiltration and circulation, colonization, dormancy, and reactivation. It further categorizes cancer bone metastasis into osteolytic and osteoblastic types. By reviewing prior research on the influence and regulation of exercise on cancer bone metastasis, this paper summarizes human and animal evidence-based studies on exercise interventions for cancer bone metastasis. It discusses exercise prescriptions for patients with such metastasis. Furthermore, from a microscopic perspective, it summarizes exercise's multi-mechanistic regulatory effects on the tumor microenvironment. Exercise regulates the tumor microenvironment through diverse mechanisms, including modulation of endocrine-paracrine signaling and immune system function. In inhibiting cancer bone metastasis, exercise further suppresses tumor formation, growth, and dissemination through multiple pathways, including altering mechanical loading, regulating endocrine-paracrine activity and immune function, and optimizing metabolic status. This provides essential non-pharmacological strategy references for cancer bone metastasis intervention and offers a basis for optimizing subsequent clinical

exercise intervention protocols and advancing related research.

1 Overview of cancer bone metastasis

Bone metastasis is a common complication of solid tumors, frequently observed in advanced malignancies such as prostate cancer, breast cancer, lung cancer, and renal carcinoma^[3]. It may be categorized into three types: osteoblastic, osteolytic, and mixed. While prostate cancer primarily manifests as osteoblastic bone metastases, most other tumors exhibit mixed osteolytic and osteoblastic changes^[11]. Cancer bone metastasis is a complex, multi-stage process that primarily encompasses: tumor cell seeding within the bone marrow, adaptation to the microenvironment, niche establishment, disruption of bone homeostasis through tumor cell-osteocyte interactions, and the release of pro-tumor growth signals during bone matrix resorption^[12] (Figure 1). Bone metastases carry significant clinical harm, with patients frequently facing heightened risks of bone-related events, including osteoporosis, pathological fractures, the need for skeletal radiotherapy or surgery, spinal cord compression, and hypercalcemia.

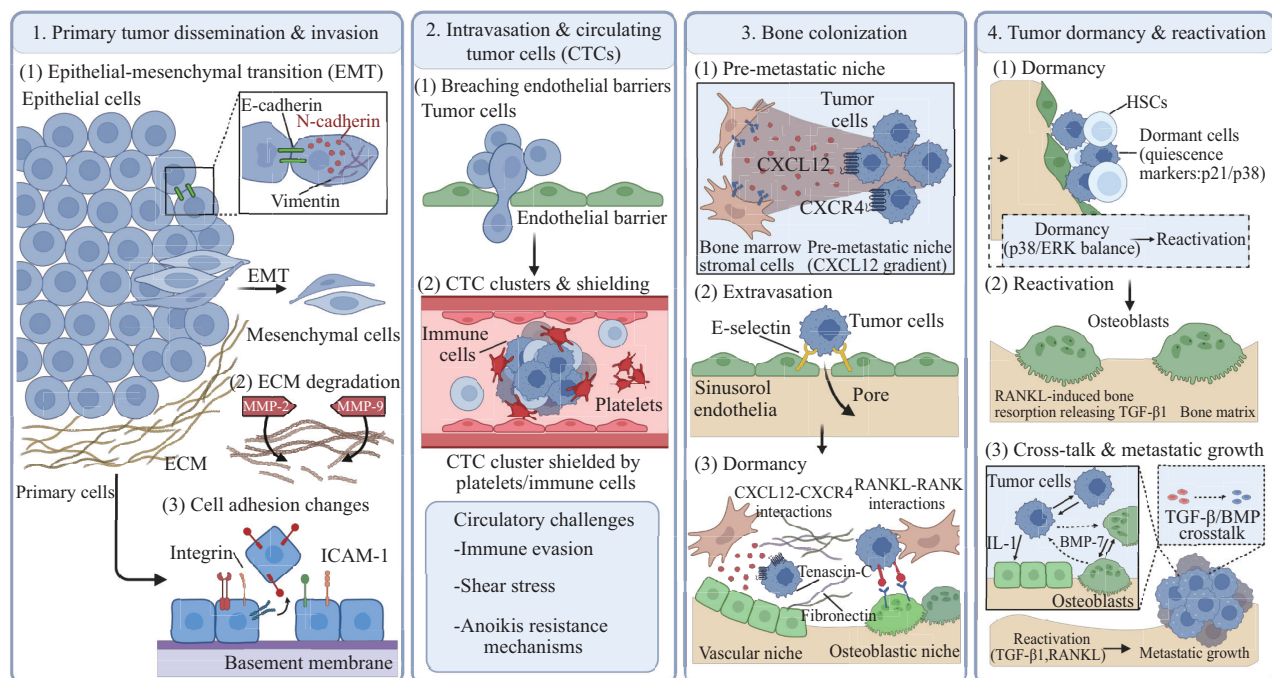


Fig. 1 The process of cancer metastasis to bone

Cancer bone metastasis involves several stages: the detachment and invasion of tumor cells from the primary tumour; intravasation, extravasation and circulation; implantation; dormancy; and reactivation. This figure was created with BioRender. EMT: epithelial-mesenchymal transition; ECM: extracellular matrix; ICAM-1: intercellular adhesion molecule-1; CTCs: circulating tumor cells; CXCL12: C-X-C motif chemokine ligand 12; CXCR4: C-X-C chemokine receptor type 4; RANKL: receptor activator of nuclear factor kappa-B ligand; RANK: receptor activator of nuclear factor kappa-b; HSCs: hematopoietic stem cells; p21: cell-cycle suppressor cyclin-dependent kinase inhibitor 1; p38: p38 mitogen-activated protein kinase; TGF-β1: transforming growth factor-β1; IL-1: interleukin-1; BMP-7: bone morphogenetic protein 7.

1.1 The process of cancer metastasis to bone

Cancer bone metastasis is a complex, multi-stage process involving dynamic interactions between tumor cells and the bone microenvironment. This process not only leads to skeletal lesions but also significantly impacts patients' quality of life and survival prognosis^[13]. It is often described metaphorically as the "seed and soil" hypothesis, illustrating the selective colonization and growth of tumor cells ("seeds") within specific organ microenvironments ("soil")^[12]. The process primarily comprises the following stages: detachment and invasion of tumor cells from the primary tumor; intravascular, extravasation and circulation; colonization; dormancy; and reactivation^[14].

1.1.1 Tumor cell detachment from the primary tumor and invasion

Tumor cells detaching from the primary tumor site and invading surrounding tissues constitute both the critical initiating phase of tumor metastasis and the primary cause of death in cancer patients^[15]. This complex process involves alterations in cancer cell characteristics and their interactions with the tumor microenvironment (TME), representing a multi-step, multi-factor-regulated cascade^[16]. Specifically, this process encompasses epithelial-mesenchymal transition in tumor cells, loss of intercellular adhesion, and degradation of the extracellular matrix.

First, tumor cells undergo epithelial-mesenchymal transition (EMT). EMT is a biological process in which epithelial cells lose polarity and intercellular junctions, acquiring the migratory and invasive capabilities of mesenchymal cells^[17]. During tumor progression, EMT facilitates the detachment of tumor cells from the primary site, transforming them into a more invasive phenotype. Key changes include downregulation of epithelial markers (*e.g.*, E-cadherin) and upregulation of mesenchymal markers (*e.g.*, N-cadherin, vimentin)^[18]. Subsequently, tumor cells alter their adhesive properties. Tumor cells modify interactions with surrounding cells and the extracellular matrix by regulating the expression of cell surface adhesion molecules (*e.g.*, integrins, selectins)^[19]. Subsequently, tumor cells alter their adhesive properties. Tumor cells modify interactions with surrounding cells and the extracellular matrix by regulating the expression of cell-surface adhesion molecules (*e.g.*, integrins, selectins)^[20]. Finally, to detach from the primary tumor and invade surrounding tissues, tumor cells must degrade the extracellular matrix (ECM). Matrix metalloproteinases (MMPs), particularly MMP-2 and MMP-9, play a pivotal role in this process by

degrading ECM components to form migration pathways^[21].

1.1.2 Intravascular permeability and circulation

After detaching from the primary tumor site, tumor cells penetrate the vascular endothelium to enter the bloodstream, a process termed intravasation^[22]. Once they enter the circulatory system, these cells are called circulating tumor cells (CTCs). During circulation, CTCs face multiple challenges, including blood flow shear stress, immune system attacks, and apoptosis due to loss of cell-matrix adhesion (*i.e.*, programmed cell death triggered by the absence of cell-matrix connections)^[23]. To survive in circulation, CTCs form aggregates and build protective barriers through interactions with immune cells and matrix cells (such as platelets, monocytes, and neutrophils), thereby resisting blood flow shear forces and immune surveillance^[24].

1.1.3 Tumor cell colonisation

The process of tumor cell bone implantation primarily comprises the following steps: establishment of pre-metastatic niches that attract CTCs to the skeleton; extravasation and homing of CTCs within pre-metastatic niches, followed by binding to bone extracellular matrix proteins; maintenance of tumor cell survival within vascular and osteoblast niches, transitioning to a quiescent state through specific adhesion interactions with host cells^[25].

The establishment of a pre-metastatic niche is the initial step in bone metastasis and involves multiple mechanisms^[26]. Tumor cells not only exploit intrinsic molecular mechanisms within the bone marrow but also promote their colonization by acting on stromal cells or osteocytes *via* soluble factors secreted by the primary tumor^[27-28]. At the same time, C-X-C motif chemokine ligand 12 (CXCL12) and C-X-C chemokine receptor type 4 (CXCR4) maintain tumor cells within the perivascular environment and regulate their extravasation from the bone marrow^[29]. Following extravasation, CTCs undergo homing, adhering specifically to proteins in the bone extracellular matrix^[30]. Among these, tenascin C, periostin, and fibronectin mediate tumor cell attachment to the bone matrix by binding to their corresponding integrin receptors^[31]. Following extravasation and homing, tumor cells may not immediately proliferate to form macroscopic metastatic lesions. Instead, they can enter a dormant state, maintaining survival within specific skeletal microenvironments to establish micrometastases^[32]. Within the skeletal microenvironment, the vascular niche (VN) and osteoblast niche (ON) are critically

implicated in sustaining tumor cells^[33]. In VN, vascular endothelial cells and their surrounding cells promote angiogenesis by secreting factors such as vascular endothelial growth factor and fibroblast growth factor, thereby supplying oxygen and nutrients to tumor cells and supporting their survival and proliferation^[34]. Tumor cells may further exploit this process to enhance their own proliferation and dissemination within bone tissue^[35]. In ON, osteoblasts, acting as bone-forming cells, secrete multiple factors, including osteopontin, osteocalcin, and insulin-like growth factor 1, which under specific conditions support tumor cell survival and dormancy^[36-37]. Consequently, tumor cells may maintain quiescence or dormancy through specific adhesion interactions with host cells^[37]. Concurrently, signaling molecules such as interleukin-1 (IL-1), secreted by breast tumor cells, act on osteoblasts, prompting them to secrete CXCL12 further, thereby attracting tumor cells *via* CXCR4-mediated pathways^[38]. Furthermore, osteoblast-secreted receptor activator of nuclear factor kappa-B ligand (RANKL) activates osteoclasts, promoting bone resorption and releasing growth factors that accelerate cancer cell growth and bone metastasis processes^[39].

1.1.4 Tumor cell dormancy

Tumor cell dormancy refers to cell-cycle arrest, also termed mitotic quiescence or cellular dormancy, and encompasses two distinct modes^[40]. The first mode involves tumor cells in the bone marrow that compete with hematopoietic stem cells (HSC) for vascular and endothelial niches. Upon entering these niches, tumor cells may enter a dormant state and resume proliferation only when the microenvironment becomes favorable^[41]. The second mode concerns the dormancy of metastatic tumor nodules, characterized by a dynamic equilibrium between cell proliferation and apoptosis, typically attributed to immune surveillance and inadequate blood supply^[42]. The signaling pathways regulating tumor nodule dormancy remain unclear, with the primary obstacle being the lack of suitable animal models that simulate tumor dormancy within the bone microenvironment. In breast cancer, tumor cell dormancy is governed by the balance between extracellular signal-regulated kinase (ERK) and p38 mitogen-activated protein kinase (MAPK) activity: ERK1/2 phosphorylation promotes proliferation, whereas p38 activation induces dormancy^[42]. Within the bone marrow microenvironment, leukemia inhibitory factor (LIF) emerges as a pivotal regulator of breast cancer cell dormancy. By binding to its receptor LIFR, LIF negatively modulates signal transducer and activator

of transcription 3 (STAT3) activity; disruption of LIFR or STAT3 expression reverses dormancy, driving breast cancer cell proliferation and promoting specific bone metastasis^[43]. Another critical factor is bone-derived transforming growth factor- β 1 (TGF- β 1) and TGF- β 2, which exert antagonistic effects on tumor cell dormancy in the bone marrow: TGF- β 2 promotes dormancy, whereas TGF- β 1 reverses dormancy^[42]. In prostate cancer, bone morphogenetic protein-7, secreted by bone marrow stromal cells, induces quiescence in prostate cancer stem-like cells^[44]. Among prostate cancer patients, the expression level of the bone morphogenetic protein 7 (BMP-7) receptor type-2 (BMPR2) negatively correlates with the risk of bone metastasis. BMP-7 induces quiescence in cancer stem-like cells by binding to BMPR2, activating p38 signaling pathway, and upregulating cell-cycle suppressor cyclin-dependent kinase inhibitor 1 (p21)^[45].

1.1.5 Reactivation of tumor cells

The reactivation of tumor cells in bone metastases is a complex process involving multifaceted interactions between tumor cells and the bone microenvironment, and it represents one of the key factors contributing to cancer recurrence and metastasis-related mortality^[46]. Notably, bone resorption creates favorable conditions for tumor cell reactivation. For instance, in animal models of breast cancer, ovariectomy-induced bone loss promotes the growth of disseminated hormone-insensitive breast tumor cells within bone^[47]. Similarly, in castration-induced androgen-deficient animal models, disseminated hormone-insensitive prostate tumor cells within bone significantly increased the incidence of bone metastasis^[48]. These investigations demonstrate that endocrine-induced imbalances in the bone microenvironment can stimulate the proliferation of dormant tumor cells by promoting bone resorption. *In vivo* imaging of a multiple myeloma mouse model revealed tumor cells colonizing bone niches in a dormant state; however, stimulation of osteoclast-mediated bone resorption using soluble RANKL reactivated tumor cells in the tumor-bearing animals, releasing them from their endosteal niche^[49]. This directly demonstrates that osteoclast activity and bone resorption are key drivers of tumor cell reactivation. Moreover, osteoclast-mediated bone resorption plays a vital role in the early stages of bone metastasis establishment. In mouse models of breast cancer bone metastasis, overexpression of vascular cell adhesion molecule-1 (VCAM-1) in tumor cells induces osteoclast precursor recruitment by binding to osteoclast α 4 β 1 integrin, thereby promoting osteoclast

formation and osteoclast-mediated bone resorption^[50]. This process creates a favorable niche for tumor cell colonization and subsequent growth within bone. Conversely, the bone-derived growth factor TGF- β 1, released during resorption, can terminate tumor cell dormancy, promoting rapid tumor growth *in vivo*^[42].

1.2 Classification of cancer bone metastases

Tumor cells drive metastasis to different sites within bone tissue by releasing factors that promote osteoclast formation and activation, as well as factors that stimulate osteoblast proliferation and differentiation^[51]. Consequently, bone metastases can be categorized into two types: osteolytic and osteoblastic. Research indicates that bone metastases may exhibit spatial heterogeneity, whereby a patient may develop osteolytic metastases in one skeletal site while presenting with osteoblastic or mixed metastases in another^[52].

1.2.1 Osteolytic bone metastasis

Osteolytic bone metastases are driven by osteolytic factors secreted by tumor cells, including parathyroid hormone-related protein (PTHrP), interleukin-11 (IL-11), and Jagged1, which collectively mediate bone destruction^[53]. PTHrP, a tumor-derived product, shares high structural and functional homology with parathyroid hormone and is the primary mediator of malignant tumor-associated hypercalcemia^[54]. PTHrP primarily enhances osteoclast activity indirectly by binding to the parathyroid hormone 1 receptor (PTH1R) on osteoblasts. PTHrP and IL-11 promote local RANKL production in bone tissue, thereby stimulating osteoclast formation and activation. Jagged1 directly binds to monocytes, facilitating osteoclast precursor fusion and participating in osteolytic bone metastasis^[55]. Breast cancer, a common osteolytic metastatic malignant tumor, expresses multiple osteolytic factors, including IL-11, connective tissue growth factor (CTGF), CXCR4, and MMP1. These factors act at distinct stages of the metastatic cascade, collectively inducing bone resorption^[56]. IL-11 regulates osteoclast generation and activity, causing bone resorption; CTGF promotes angiogenesis, tumor growth, and osteoblast proliferation; MMP1 enhances cancer cell invasiveness and further amplifies this process by activating the RANK/RANKL signaling pathway^[53]. Additionally, the Wnt signaling pathway plays a crucial role in breast cancer bone metastasis by maintaining tumor stem cell activity and interacting with IL-1 β ^[57]. Beyond endogenous stimuli, *ex vivo* pharmacological interventions, such as

β 2-adrenergic receptor (β 2-AR) activation, also promote breast cancer cell migration independently of the CXCL12-CXCR4 axis. These migratory effects may be impeded by β -AR blockade or RANKL inhibition^[58].

1.2.2 Osteoblast bone metastasis

Osteoblastic bone metastasis is a complex pathological process characterized by abnormal osteoblast proliferation and differentiation, leading to the formation of new bone^[59]. This process is associated with the production of multiple osteogenic factors, including endothelin-1, growth differentiation factor 15, and osteomorphin, which are mediated by the Wnt signaling pathway. Collectively, these factors promote osteoblast proliferation and differentiation^[60].

Osteoblast precursor cells within the bone microenvironment are considered the primary cellular source of tumor-induced bone formation. The Wnt signaling pathway plays a pivotal role in skeletal development and in maintaining bone homeostasis, promoting osteoblast proliferation and differentiation by regulating the expression of osteogenic factors such as endothelin-1 (ET-1), growth differentiation factor 15 (GDF15), and BMPs^[61]. In prostate cancer bone metastasis, activation of the Wnt signaling pathway and tumor-derived ET-1 stimulate fibroblast growth factor receptors, inducing abnormal new bone formation^[62]. Tumor cells can induce osteoblasts to secrete GDF15, thereby promoting prostate cancer growth and invasion and creating a microenvironment conducive to tumor progression^[63]. BMPs, members of the transforming growth factor- β superfamily, play a central regulatory role in bone formation and repair. BMPs secreted by tumor cells or other cells within the bone microenvironment can induce mesenchymal stem cells to differentiate into osteoblasts, thereby participating in the initiation and progression of osteoblastic bone metastasis^[64]. Research indicates that prostate tumor cells can displace HSC from their bone marrow niche, thereby creating favorable microenvironmental conditions for bone metastasis^[65]. The process by which prostate tumor cells occupy the HSC niche may also maintain tumor cell dormancy^[66]. Further investigations revealed that tumor-associated endothelial cells derived from mouse prostate cancer express HSC and mesenchymal stem cell markers, differentiate into cartilage and bone, and upregulate SRY-box transcription factor 9 (SOX9) and osteocalcin (OCN)^[67]. This process further promotes intravascular formation within bone, thereby accelerating tumor cell infiltration.

2 Evidence-based research on exercise interventions for cancer bone metastases

2.1 Human studies on exercise interventions for cancer bone metastases

Exercise can enhance physical function in cancer patients by improving cardiorespiratory fitness, muscular strength, and body composition^[68]. Furthermore, exercise is significantly associated with higher survival rates among cancer patients, particularly those with breast and prostate cancer^[69]. Research indicates that exercise plays a crucial role in improving bone health in cancer patients, with mechanisms that may include regulation of bone remodeling, matrix mineralization, and bone mineral density (BMD)^[70]. Recent research on exercise and bone health in cancer patients with bone metastases has primarily focused on populations with breast cancer, prostate cancer, and mixed cancer bone metastases. Most findings indicate that exercise interventions lead to significant increases in overall or metastatic bone mineral density, along with a marked reduction in pathological fracture incidence (Table 1).

Currently, evidence on exercise improving bone health in patients with cancer bone metastases remains limited. Bjerre *et al.*^[71] conducted a six-month football exercise intervention in 41 patients with prostate cancer bone metastases, finding no significant changes in total bone mineral density at the hip or spine. Uth *et al.*^[72] conducted a six-month football exercise intervention in 57 patients with

advanced or metastatic prostate cancer. They observed an increase in total or leg bone mineral density, suggesting exercise may positively influence bone mass. Furthermore, exercise can directly improve bone damage and promote remineralization. An isometric resistance exercise intervention study involving 60 patients with spinal metastases demonstrated increased bone density at metastatic sites and a significant reduction in pathological fracture rates^[73]. Another study compared the effects of exercise on bone density at metastatic sites during radiotherapy for spinal metastases. After completing resistance training 5 d per week for two weeks, followed by home-based resistance training three times weekly for 6 months, patients showed improved BMD at spinal metastatic sites and significantly reduced expression of bone metastasis markers (*e.g.*, pyridinoline and type I collagen C-terminal cross-linking peptide) compared to the control group. These findings suggest exercise may synergistically enhance radiotherapy outcomes by promoting recalcification of bone metastases^[74]. In summary, exercise may improve bone health in cancer patients with skeletal metastases by modulating bone mineral density, reducing pathological fracture risk, and regulating the expression of bone metastasis markers. However, existing evidence requires further validation through additional studies, alongside the development of appropriate tools to assess the feasibility and applicability of exercise interventions in this population.

Table 1 Human studies on exercise interventions for cancer bone metastases

Research subjects	Sample size (<i>n</i>)	Exercise program	Result	Reference
Patients with metastatic breast cancer	357	A structured and personalised exercise programmer, 2 times/ week, 1 h/session, 9 months	No change in BMD following exercise	[75]
Patients with mixed cancers	60	Supervised resistance training, 5 sessions/week, 2 weeks. Followed by unsupervised home resistance training, 3 sessions/week, 6 months	Increased bone mineral density at the transfer site; no changes in bone survival, progression-free survival, or pathological fractures	[76-78]
Breast cancer patients	100	Moderate-intensity aerobic exercise and resistance training, 2 times/week, 16 weeks	Post-exercise BMD increased; OCN expression increased	[79]
Breast cancer patients	43	Aerobic exercise, 2–5 times/week, 20–60 min/session, sustained over 24 weeks. Moderate-to-low intensity resistance training, 2–3 times/week, 8–10 repetitions/set, sustained over 24 weeks	Post-exercise BMD increased; femoral neck BMD decreased	[63]
Patients with spinal metastases	60	Supervised resistance training, 5 times/week, 2 weeks. Home-based resistance training, 3 times/week, 6 months	Improvement in bone mineral density at metastatic sites and in bone with osteolytic lesions	[74]

Continued to Table 1				
Research subjects	Sample size (n)	Exercise program	Result	Reference
Patients with advanced prostate cancer	57	Football training 2 or 3 times/week, 12 weeks	Increase in bone mineral content and type I procollagen N-terminal propeptide	[72]
Patients with advanced prostate cancer	57	Football training 2 or 3 times/week, 32 weeks	Increases were observed in bone mineral density at the hip joint and femoral shaft, alongside elevated levels of osteocalcin	[80]
Prostate cancer patients	154	Aerobic exercise, 2 times/week for 20–30 min at 60%–85% of maximum heart rate, combined with resistance training 2 times/week, using 6–12 repetitions at maximum RM, sustained for 12 months	Increased BMD in the spine and femoral neck, with reduced bone loss in the spine	[81]
Breast cancer patients	573	Moderate to vigorous aerobic exercise per week, 3–4 sessions/week	Reduce bone loss in the femoral neck	[82]
Breast cancer patients	154	Aerobic exercise, 3 times/ week for 30 min each session at 65%–70% of maximum heart rate, 12 weeks. Resistance training, 3 times/week with 8 repetitions/set, 12 weeks	Promotes bone remodelling, with no change in BMD	[83]
Prostate cancer patients	51	Moderate-intensity aerobic exercise, 150 min/week. Resistance training should aim for 2 to 3 sets of 9 exercises, repeating 8 to 15 times, 2 to 3 times weekly	Improvement in BMD at L1-L4 and the entire hip region	[84]
Prostate cancer patients	96	Moderate to high-intensity endurance exercise	Improvement in hip DEXA score	[85]
Prostate cancer patients	214	Football training, 2 times/week, 6 months	Increased hip BMD	[86]
Breast cancer patients	206	Aerobic exercise, 3 sessions/week of lasting 20–30 min each, combined with 3 sessions /week of resistance training comprising 8–12 repetitions/set, 1 year	Preventing bone loss, bone turnover markers have all decreased	[87]
Patients with mixed cancers	60	Supervised resistance training 5 times/week. Home resistance training 3 times/week, 6 months	Improvement in BMD at the transfer site and in pathological fractures	[72]
Breast cancer survivor	41	Home-based aerobic and progressive resistance exercise programme EXCAP®™ 12-week exercise intervention period, 7 d/week	Exercise failed to improve skeletal biomarkers	[88]
Breast cancer survivor	121	An average of 54.8 min of aerobic and resistance exercise per week, 12 months	No change in BMD following exercise	[89]
Breast cancer survivor	223	Engage in ST exercise 2 times/week for 30–45 min/session, 24 months	Improvement in BMD throughout the hip and spine	[90]
Prostate cancer patients	70	Resistance training, 2 times/week. Home resistance training, 1 time/week, 12 months.	Post-exercise BMD increased	[91]
Patients with metastatic prostate cancer	57	Aerobic and resistance training, 3 times/week, 3 months	Post-exercise BMD increased	[92]

BMD: bone mineral density; OCN: osteocalcin; DEXA: dual-energy X-ray absorptiometry; EXCAP®™: exercise and cancer adaptive platform; ST: strength training.

2.2 Animal studies on exercise intervention for cancer bone metastasis

Presently, animal studies investigating exercise interventions for cancer bone metastases primarily focus on moderate-intensity aerobic exercise and

mechanical loading stimulation in mice. Research by Liu *et al.* [93] demonstrated that aerobic exercise inhibits the progression of both local and distant tumours in breast cancer mice and mitigates tumour-induced bone destruction. Another study showed that

applying mechanical loading stimulation at 0.3 g @ 90 Hz for 15 min daily over eight weeks to mice with bone metastases increased trabecular bone volume fraction (the percentage of total volume occupied by bone tissue, BV/TV), elevated cortical bone volume, and significantly improved bone loss^[94]. Presently, animal studies investigating exercise interventions for cancer bone metastases remain limited. The precise

mechanisms of action remain unclear, and reference exercise protocols are scarce. Existing evidence indicates that exercise is safe and feasible for cancer patients with bone metastases, osteoporosis/osteopenia, or at risk of bone loss. Furthermore, exercise improves skeletal health, physical function, and quality of life, while helping manage the cancer itself and treatment-related adverse effects (Table 2).

Table 2 Animal studies on exercise interventions for cancer bone metastases

Research subjects	Exercise modality	Exercise intensity	Result	Reference
Lung cancer mouse model	Moderate-intensity aerobic exercise	9 m/min, 30 min/d, 5 d/week, over a period of 4 weeks	Inhibit the progression of bone metastasis	[93, 95]
Breast cancer mouse model	Moderate-intensity treadmill exercise and mechanical loading	16 m/min, 50 min/d, 5 d/week for 5 weeks. 4.5 N, 630 μ e, 4 Hz, 300 cycles/d, 5 d/week for 4 weeks	Inhibited tumour-induced bone destruction	[96]
Ovarian cancer mouse model	Low-intensity mechanical loading	15 min/d, 5 d/week, 1 year	Reduced bone mass without affecting the mice's life expectancy	[97]
Mice with bone metastases	Mechanical loading	15 min/d, 0.3 g, 90 Hz, 8 weeks	The bone trabecular volume fraction (BV/TV) increased, cortical BV rose, and bone loss was inhibited	[94]
Breast cancer mouse model	Treadmill training	20 m/min, 60 min/d, 5 d/week, 35 weeks	Reduced the number of palpable breast tumours and palpable masses	[98]
Breast cancer mouse model	Treadmill running and localised tibial loading	10 m/min, 30 min/d, 5 d/week; 15 m/min, 30 min/d, 5 d/week; 20 m/min, 30 min/d, 5 d/week	Moderate (low to medium) intensity significantly inhibits tumour-induced bone destruction, reduces osteoclast activity, and enhances osteoblast survival; excessively high intensity, conversely, accelerates bone loss, exhibiting a J-shaped curve relationship	[99]

BV/TV: the percentage of total volume occupied by bone tissue.

Based on the data summarized in Tables 1, 2, exercise interventions demonstrate a “definite but limited” efficacy against cancer bone metastases, with their primary value lying in serving as an adjunctive approach to improve bone health. This efficacy exhibits clear tumor-specific and exercise-type-specific characteristics. Regarding tumor types, exercise provides superior bone protection for patients with prostate cancer compared to those with breast cancer. As for exercise modalities, moderate to low-intensity exercise yields the best results, particularly resistance training and mechanical load training, while the animal experiments presented in Table 2 suggest that high-intensity exercise may accelerate bone loss.

2.3 Reflections on exercise prescriptions for patients with cancer bone metastases

Exercise is a key approach to cancer prevention and treatment, improving physical function in cancer patients and alleviating related side effects^[100].

Research indicates that exercise can also enhance physical function in patients with bone metastases^[101]. For most cancer patients, moderate-to-vigorous, multimodal exercise is generally appropriate; however, no fixed exercise prescription or volume has been proven suitable for all cancer patients^[102]. The optimal exercise prescription for cancer patients with bone metastases remains undefined. Current practice primarily follows the 2019 American College of Sports Medicine guidelines for exercise in cancer patients. These guidelines recommend 90 min of aerobic exercise per week, with each session lasting at least 30 min, combined with resistance training twice weekly. This involves performing two sets of moderate-intensity exercises, each repeated 8–15 times.

In addition to exercise guidelines for cancer patients, individuals with osteoporosis may incorporate balance training to improve dynamic equilibrium and reduce the risk of falls, thereby

reducing fracture risk^[103]. However, exercise prescriptions must be tailored to the individual, considering both the effects of exercise on bone remodeling and safety concerns. For instance, in aerobic exercise, treadmill running promotes bone anabolism more effectively than cycling but carries a higher risk of falls. In resistance training, free-weight and high-intensity resistance exercises more effectively increase mechanical loading on bones but carry greater injury risks. Isometric exercises or resistance training using elastic bands more effectively promote bone formation. Thus, exercise prescriptions should select appropriate programs based on patient circumstances, with suitable monitoring and timely adjustments. Most cancer patients present with compromised physical condition; exercise should commence at low intensity and gradually increase over several weeks based on the patient's physiological response. For patients with bone metastases, exercise prescription requires a comprehensive assessment by oncology and exercise specialists of metastatic sites and fracture risk. Only then can a personalized exercise plan be developed, selecting appropriate exercise modalities with suitable frequency and intensity to avoid overloading metastatic sites.

3 Possible mechanisms of exercise inhibition of cancer bone metastasis

As research into the mechanisms of tumor metastasis continues to advance, exercise—as a non-pharmacological intervention—is garnering increasing attention from the scientific community for its positive role in inhibiting tumor progression and bone metastasis. Exercise modulates the tumor microenvironment through multiple mechanisms, including alterations in mechanical loading and endocrine-paracrine activity, as well as regulation of immune and metabolic processes, thereby suppressing tumor formation, growth, and spread (Figure 2).

Specifically, at the mechanical load level, the mechanical signals generated by exercise can directly act on osteocytes within the bone microenvironment. As the primary mechanoreceptors, osteocytes suppress tumor cell extravasation and bone metastasis by regulating endothelial cell permeability and osteoclast activity in response to mechanical stimulation^[104]. At the endocrine-paracrine level, exercise can alter the miRNA profile carried by extracellular vesicles and particles (EVPs) in the circulation, such as upregulating *miR-486* and *miR-34b*. These miRNAs inhibit tumor cell proliferation,

migration, and invasion by targeting cell cycle-related genes and oncogenes^[105]. Regarding immune remodeling, exercise not only enhances the cytotoxic activity of antitumor immune cells, promotes the infiltration of antitumor immune cells into the tumor and bone marrow microenvironments, and suppresses the accumulation of immunosuppressive cells^[106], but also transforms the immunosuppressive microenvironment into one conducive to antitumor immune responses by improving oxygenation in tumor tissues and downregulating pro-inflammatory factors^[107]. Furthermore, at the metabolic intervention level, exercise limits energy uptake by tumor cells by enhancing insulin sensitivity and lowering blood glucose and plasma insulin levels, while simultaneously increasing fatty acid oxidation to reduce the lipid substrates on which tumors depend^[108]. This systemic metabolic shift creates a “metabolic barrier” in distant organs, limiting the establishment of metastatic foci through competition for nutrients between normal tissues and tumor cells.

3.1 Mechanical load

Mechanical load is widely recognized as a regulator of cancer cell proliferation and migration, as multiple mechanical loads are exerted on organs such as bone during movement^[109]. Numerous *in vitro* studies employ simulated skeletal signals, including oscillating fluid or dynamic compression. Meta-analyses indicate that applying mechanical loads to the body significantly inhibits the activity, proliferation, and carcinogenic potential of breast tumor cells^[110]. Intraosseous mechanical signals modulate interactions between metastatic tumor cells and osteocytes. As the primary mechanical sensors in bone, osteocytes suppress tumor cell metastasis and dissemination in response to mechanical loading^[111].

Research has shown that culturing six types of mouse and human breast tumor cells in osteoblast-conditioned medium under mechanical loading promotes cancer cell migration while inhibiting proliferation^[112]. This indicates that mechanical loading of osteoblasts can indirectly influence metastatic tumor cells. Further studies suggest that the anti-metastatic potential of osteoblasts stimulated by blood flow-induced mechanical loading is mediated by osteoclasts and endothelial cells^[113]. Specifically, culturing M. D. Anderson-metastatic breast cancer 231 (MDA-MB-231) cells in osteoblast-conditioned medium stimulated by mechanical loading increased their migration while reducing apoptosis. Conversely, culturing endothelial cells in osteoclast-conditioned medium or osteoblast-conditioned medium under mechanical loading inhibited breast cancer cell

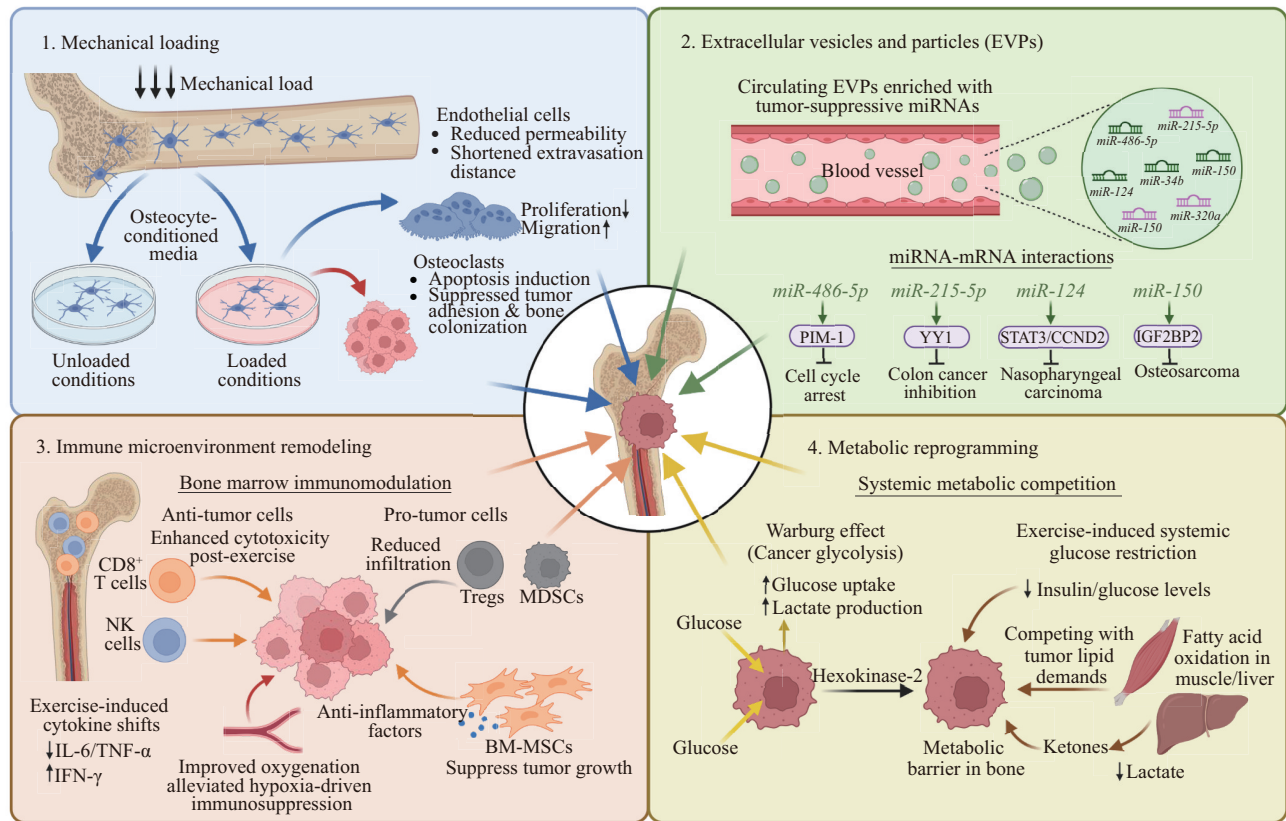


Fig. 2 Mechanisms of exercise inhibition of cancer bone metastasis

Exercise modulates the tumour microenvironment through multiple mechanisms, including altering mechanical loading and endocrine-paracrine activity, and regulating immunity and metabolism, thereby suppressing tumour formation, growth, and dissemination. This figure was created with BioRender. EVPs: extracellular vesicles and particles; CD8⁺: CD8⁺ cytotoxic; NK: natural killer; BM-MSCs: bone marrow mesenchymal stem cells; IL-6: interleukin-6; TNF-α: tumor necrosis factor-α; IFN-γ: interferon-gamma; IGF2BP2: insulin-like growth factor 2 mRNA-binding protein 2; PIM-1: proviral insertion site of moloney murine leukemia virus-1; STAT3: signal transducer and activator of transcription 3; CCND2: cyclin D2; YY1: Yin Yang 1.

migration and promoted apoptosis^[113]. The mechanism involves mechanically stimulated osteoblasts reducing endothelial cell permeability, inhibiting breast cancer cell adhesion to endothelial monolayers, shortening extravasation distances, and downregulating the potential for cancer bone metastasis *via* indirect signaling through endothelial cells^[114]. As can be seen, under mechanical loading, the regulatory role of the bone microenvironment on tumors exhibits “cell-type dependence”: while osteoblasts acting alone may promote tumor cell migration, the overall effect becomes inhibitory upon the introduction of osteoclasts or endothelial cells. However, other studies have reported findings contrary to the above findings, potentially attributable to experimental variations, such as mechanical loading methods (steady versus oscillatory flow) and the use of cell lines at different stages (early versus mid-stage)^[115]. For instance, one study demonstrated

that mechanically stimulated osteoblasts reduce endothelial cell permeability, thereby inhibiting breast cancer cell adhesion to endothelial monolayers and shortening extravasation distances. Concurrently, through indirect signaling *via* endothelial cells, they downregulate the potential for cancer bone metastasis. This research suggests that osteocytes, in response to mechanical loading, can influence cancer cell metastatic behavior by regulating other cell types, such as endothelial cells and osteoclasts^[113]. Among these, low-intensity vibration (LIV), a non-invasive form of mechanical stimulation, has demonstrated potential to inhibit tumor growth and preserve bone integrity^[116]. In both *in vivo* multiple myeloma models and aged mice with spontaneous granulosa cell ovarian carcinoma, low-intensity vibration restricted tumor growth while preserving bone integrity^[97]. For patients with bone fragility, particularly those with cancerous bone metastases, low-intensity vibration

could serve as a safe alternative to exercise, though the precise methodology remains to be determined. Future exploration of non-invasive mechanical stimuli, such as low-intensity vibration, for cancer bone metastasis treatment could offer novel alternatives for patients with limited mobility and high fracture risk. LIV not only inhibits cancer cell migration but also induces tumor-suppressing cell generation, demonstrating potential *in vivo* to restrict tumor growth and preserve bone integrity. This may provide additional options and strategies for future exercise rehabilitation in patients with bone metastasis^[116]. Therefore, LIV is not merely a physical intervention; it represents a therapeutic approach that reshapes the antitumor niche by modulating cellular communication within the bone microenvironment. In summary, exercise exerts effects on the bone microenvironment through mechanical loading, regulating interactions between osteocytes and cancer cells while inhibiting cancer bone metastasis by modulating cell types such as endothelial cells and osteoclasts. Although specific mechanisms remain under investigation, the potential of mechanical loading to prevent and treat bone metastasis is increasingly evident. Non-invasive interventions, particularly low-intensity vibration, offer novel directions for future clinical interventions.

3.2 Extracellular vesicles and granules

Changes in several miRNAs within circulating extracellular EVPs after exercise contribute to tumor growth and metastasis. Exercise-induced alterations in circulating EVPs miRNAs and the subsequent suppression of downstream targets—such as cyclin and cyclin-dependent kinase (CDK) mRNAs—correlate with negative regulation of the cell cycle in recipient tumor cells^[117]. Both preclinical and clinical evidence indicate elevated *miR-486* levels in the circulating EVPs of exercised mice^[97]. Similarly, elevated levels of total circulating *miR-486* were observed in non-exercising athletes^[118]. Notably, increased *miR-486* expression significantly reduced breast cancer cell proliferation and induced G1 arrest by targeting the oncogene proviral insertion site of moloney murine leukemia virus-1 (PIM-1). Furthermore, *miR-486* inhibited the growth of breast cancer xenograft tumors in nude mice^[119]. Compared with sedentary individuals, baseline levels of *miR-215-5p* in circulating EVPs were elevated in elderly males following both regular and acute exercise^[106]. *In vitro* studies by Chen *et al.*^[120] showed that *miR-215* mimics suppressed cell proliferation, migration, and invasion in human colon tumor cells. The anti-tumor mechanism of *miR-215* may involve reduced Yin

Yang 1 (YY1) expression. Further research indicates that circulating EVPs *miRNA-124* is upregulated following high-intensity interval exercise, subsequently inhibiting STAT3, p-STAT3, G1/S-specific cyclin D2, and ECM, thereby impeding proliferation, migration, and invasion in C666-1 tumor cells^[121]. Furthermore, studies confirm that, post-exercise, *miR-34b* levels in circulating EVPs of elderly populations increase immediately^[106]. *In vitro* and *in vivo* evidence indicate that *miR-34*-containing exosomes derived from cancer-associated fibroblasts can inhibit the progression and development of gastric cancer. Dimassi *et al.*^[121] observed elevated circulating EVP *miR-150* levels in normal-weight or overweight adult Caucasian women following a high-intensity interval aerobic exercise program. Consistent with this, *miR-150* expression was significantly reduced in osteosarcoma tissue compared to adjacent non-cancerous tissue, while expression of its direct target, insulin-like growth factor 2 mRNA-binding protein 2, was markedly elevated in osteosarcoma tissue. Another miRNA potentially associated with reduced cell invasion and migration is *miR-320a*. Interestingly, circulating EVPs exhibit increased *miR-320a* following aerobic exercise^[88]. As a tumor suppressor in gliomas, *miR-320a* upregulation inhibits c-Myc, thereby modulating cellular proliferation and invasive processes^[122]. This suggests that exercise-induced regulation of the *miR-320a*/c-Myc axis represents another potential molecular pathway for inhibiting the progression of malignant tumors such as gliomas. Exercise-induced alterations in circulating EVPs miRNAs offer novel perspectives for cancer prevention and treatment. Future investigations into the specific molecular mechanisms of these miRNAs and their roles across different cancer types may facilitate the development of exercise-based, personalized cancer intervention strategies.

3.3 Immune environment

The regulation of immune microenvironment in cancer bone metastases by exercise is a complex, multifaceted process. Its core mechanism involves altering the composition and functional state of immune cells within the bone marrow microenvironment (BMM), thereby influencing tumor cell seeding, growth, and progression within skeletal tissue^[123]. Under steady-state conditions, substantial numbers of immune cells reside within the bone marrow^[124]. Tumor-infiltrating immune cells comprise two distinct types: tumor-antagonistic and tumor-promoting cells, with some exhibiting dual phenotypes. Cells exhibiting anti-tumor activity are primarily composed of CD8⁺ T cells, natural killer

(NK) cells, $\gamma\delta$ T cells, and natural killer T (NKT) cells. Cells exhibiting pro-tumor activity include regulatory T cells (Treg) and myeloid-derived suppressor cells (MDSC)^[106]. Moreover, macrophages, neutrophils, dendritic cells, CD4⁺ helper T cells, B cells, eosinophils, and basophils can perform both functions depending on their polarization or phenotype^[125]. All these cells are implicated in the initiation and progression of bone metastases.

Exercise may modulate the bone marrow immune microenvironment through multiple pathways to counteract cancer bone metastasis. Regular physical activity has been shown to enhance immune function, specifically by increasing NK cell cytotoxicity and optimizing T-cell activation and function^[125]. This immune-enhancing effect may suppress tumor cell growth within the bone marrow and eliminate metastatic lesions. For instance, CD8⁺ T cells, pivotal in tumor immunity, exhibit enhanced activity with exercise, thereby strengthening antitumor effects^[126]. Furthermore, exercise modulates the recruitment and distribution of immune cells within the bone marrow by regulating the secretion profile of cytokines and chemokines^[127]. Specifically, this regulation promotes the infiltration of antitumor immune cells (*e.g.*, CD8⁺ T cells, NK cells) into the bone marrow while suppressing the accumulation of pro-tumor immune cells (*e.g.*, Treg cells, MDSC). This transforms the immunosuppressive bone marrow microenvironment into a state with enhanced antitumor activity, thereby helping to maintain the microenvironment's antitumor response bias^[126]. Further research indicates that exercise indirectly influences bone metastasis progression by optimizing the physical and biochemical characteristics of the tumor microenvironment^[122]. Hypoxic conditions constitute a significant driver of tumor immunosuppression, impairing T-cell function and promoting MDSC aggregation^[126]. Exercise improves tumor oxygenation, creating conditions conducive to the effective functioning of antitumor immune cells. Concurrently, exercise exerts anti-inflammatory effects by downregulating the expression of pro-inflammatory cytokines (such as interleukin-6 (IL-6), and tumor necrosis factor- α (TNF- α)) within the bone marrow microenvironment, thereby diminishing support for tumor cell growth^[126]. Moreover, exercise may regulate stromal cell function, including bone marrow mesenchymal stem cells (BM-MSC), thereby indirectly modulating the microenvironment's inflammatory state and inhibiting tumor progression^[128]. In summary, the regulatory mechanisms of exercise on cancer bone metastasis are

comprehensive and multi-layered, encompassing enhanced immune cell function, optimized immune cell recruitment and distribution, improved physical and biochemical characteristics of the tumor microenvironment, and regulation of inflammatory responses. Further investigation into the specific molecular mechanisms by which exercise regulates the bone marrow immune microenvironment, particularly its effects on distinct immune cell subsets and bone marrow mesenchymal stem cells, will contribute to a more comprehensive understanding of how exercise inhibits cancer bone metastasis.

3.4 Cancer metabolism

Metabolic reprogramming is a core characteristic of tumor cells, reflected in the adjustment of metabolic pathways to support rapid proliferation, survival, and adaptation to dynamic microenvironments^[129]. It plays a pivotal role in bone metastasis, enabling tumor cells to survive in the nutrient- and oxygen-limited microenvironment of the primary tumor site and subsequently colonize distant organs, including bone^[130].

Exercise inhibits bone metastasis by regulating systemic metabolism, particularly by remodeling glucose and lipid metabolism. Tumor cells often exhibit abnormal glycolysis, preferentially converting glucose to lactate even under aerobic conditions—a phenomenon known as the Warburg effect^[131]. Research indicates that exercise induces systemic glucose restriction by enhancing insulin sensitivity and lowering plasma insulin and glucose levels. This limits energy uptake in tumor cells within both primary tumors and metastatic sites (including bone), leading to energy deprivation and suppression of growth and proliferation^[132]. Concurrently, cancer cell growth and metastasis are highly dependent on lipid metabolism^[133]. Exercise enhances fatty acid oxidation and increases the body's utilization of fatty acids, thereby reducing the lipid substrates required for cancer cell survival and metastasis^[134]. This diminishes their adaptability within the bone marrow microenvironment. Consequently, exercise-induced systemic metabolic reprogramming limits tumor establishment and progression by increasing the nutritional demands of normal tissues, thereby competitively depriving tumor cells of nutrients and creating a “metabolic barrier” in distant organs such as bones. In summary, exercise-induced systemic metabolic reprogramming increases nutritional demands in normal tissues, competitively depriving tumor cells of nutrients and forming a “metabolic barrier” in distant organs (such as bone), thereby restricting tumor implantation and progression.

Exercise offers a multi-tiered intervention strategy for inhibiting tumor bone metastasis by systematically remodeling the body's metabolic state. Its effects extend beyond directly restricting cancer cell energy uptake and metabolic adaptability; it also activates systemic organ metabolism and competitively depletes nutrients, establishing a protective barrier within the skeletal microenvironment^[135]. This mechanism deepens our understanding of exercise's anti-tumor effects, extending beyond the traditional immune-enhancing perspective to encompass the precise regulation of the whole-body metabolic network.

4 Conclusion and future prospects

In summary, exercise shows considerable potential to inhibit cancer bone metastasis, not only by reducing cancer incidence but also by improving bone health in patients with bone metastases. Exercise inhibits bone metastasis by altering mechanical loads and modulating interactions among osteocytes, tumor cells, and other relevant cells. Furthermore, exercise induces changes in miRNAs within circulating extracellular vesicles and particles, thereby suppressing tumor growth and metastasis by regulating tumor cell processes such as cell cycle progression, proliferation, migration, and invasion. Exercise further modulates the immune microenvironment of bone metastasis by altering the composition and functional state of immune cells within the bone marrow microenvironment. This enhances anti-tumor immune responses, thereby inhibiting tumor cell seeding, growth, and progression within bone tissue. By modulating systemic metabolism—including reshaping glucose metabolism and regulating lipid metabolism—exercise offers a multi-tiered intervention strategy for inhibiting tumor bone metastasis. It forms a protective barrier within the skeletal microenvironment by restricting tumor cells' energy uptake and metabolic adaptability while competitively depriving tumor cells of nutrients.

Although the exact mechanism by which exercise inhibits bone metastases in cancer involves complex systemic circulatory, immune, and metabolic changes, it has not yet been fully elucidated, which limits the development of optimal exercise regimens and new therapies. From a clinical perspective, given the higher risk of exercise-related injuries among patients with bone metastases, there is an urgent need for highly personalized exercise prescriptions; however, existing clinical trials generally suffer from inconsistent standards and insufficient supervision.

Therefore, future research should focus on quantifying exercise regimens, clarifying dose-response relationships, and identifying measurable biomarkers; such studies will complement efforts to further elucidate the mechanisms by which exercise modulates bone metastasis.

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运动干预对癌症骨转移的作用机制*

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摘要 癌症骨转移是乳腺癌、前列腺癌等实体瘤常见的并发症, 在晚期患者中具有较高的发生率。该过程常导致骨痛、病理性骨折和高钙血症等并发症, 不仅严重损害患者的生活质量, 还可能增加死亡风险。癌症骨转移过程涵盖多个阶段, 包括肿瘤细胞从原发灶脱离与侵袭、进入血管并循环、在骨微环境中定植、休眠以及再激活等。运动作为一种潜在干预手段, 可抑制癌症骨转移、改善骨微环境并减轻相关症状, 其作用机制可能与机械负荷、细胞外囊泡与颗粒的调控, 抑制免疫与代谢途径有关。本文综述了骨转移的发病机制和分类。此外, 基于对骨转移运动干预相关的人类和动物研究的综合分析, 本文重点阐明了运动通过调节机械负荷、细胞外囊泡和颗粒, 以及通过免疫和代谢途径来抑制肿瘤形成、生长和扩散, 从而干预骨转移的机制。然而, 目前针对癌症骨转移患者的运动方式与强度选择仍较为有限, 运动处方的制定尚缺乏明确依据。本综述旨在探讨运动对癌症骨转移患者骨健康的影响, 分析运动处方制定的考量因素与注意事项, 并为该类患者运动处方的建立及相关研究的深入开展提供新思路。

关键词 癌症, 骨转移, 运动, 肿瘤

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