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Physiological Mechanisms of Exercise in Prevention and Treatment of Breast Cancer: A Review

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ABSTRACT

Background: Considering limitations related to intensity, duration, and mode of exercise and possible physiological mechanisms, this study aimed to summarize the physiological mechanisms emphasizing inflammation, angiogenesis, and immunology of different exercises related to prevention and treatment of breast cancer.

Methods: In the current review study, different platforms were analyzed including PubMed, Scopus, Cochrane, Embase, Web of Science, Science Direct, Google Scholar, and Research Gate as well as Iranian databases such as Scientific Information Database (SID) and Magiran. The data was reviewed until May 2024. Search keywords included “exercise", "sport”, “physical exercise”, “intensity, training”, “breast cancer”, “inflammation”, “angiogenesis”,” immunology”, and “physiological mechanisms”.

Results: Among several proposed mechanisms, inflammation, immunity and angiogenesis have been mentioned as important indices but there are ambiguities regarding the influence of different intensities and durations of exercise on breast cancer prevention and treatment. Other effective factors such as the effect of exercise on gene regulation and some other mechanisms have been proposed as possible mediators.

Conclusion: According to some previous studies, aerobic exercise induces positive effects on preventing and treating breast cancer through reducing inflammation, improving angiogenesis, and enhancing immunological mechanisms. Regarding duration and intensity, long term regular exercise (>8 weeks), in the form of aerobic and especially high intensity interval training (HIIT) reduces inflammation. while the effect of short-term exercise training is not clear yet and high intensity exercise may induce suppressing effects on the immune system. Therefore, the effect of intensity and duration of exercise on physiological mechanisms must be clarified.

INTRODUCTION

Breast cancer incidence rates have increased during the last four decades in the world; However, breast cancer mortality rates have decreased in recent years compared to previous decades.[1] A study reported that the rate of breast cancer in southern Iranian women had a increasing trend from 2001 to 2018, while this trend was slower during the recent years.[2] Women are particularly prone to breast cancer, which is among the widespread types of cancer and is often fatal.[3,4] Breast cancer affects 13% of women (1 in 8),[5] and the survival rate has been reported to be 49.3% at 10 years for breast cancer

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patients among Southeast Asian women.[6] Breast cancer treatment include radiation therapy, chemotherapy, and hormone therapy which can be associated with psycho-physiological symptoms that worsen the quality of life for patients.[7] Therefore, prevention, reducing progression and symptoms, and increasing the survival of patients are important issues.

Breast cancer initiation and development are accompanied with some risk factors, such as genetic/family history, age, gender, prolonged estrogen exposure, medical history of some disease such as diabetes, alcohol consumption, high body mass index (BMI), smoking,[8] exposure to radiation, low physical activity, and obesity.[9] Physical inactivity, in particular, can be the cause of some cancer cases, especially in postmenopausal women.[10]

Various interventions are available to reduce symptoms, and regular physical exercise is recommended as a prevention method for improving fatigue, pain, physical function, and muscle strength in breast cancer patients.[11] Aerobic exercise can improve cardiorespiratory capacity, physical fitness, and body composition which helps reduce symptoms[12] such as anxiety and depression and leads to an improved quality of life.[13] Also, resistance training could similarly increase quality of life, decrease fatigue, improve physical functioning and bone health and reduce lymphedema. Concurrent aerobic and resistance exercises have been reported to reduce anxiety, fatigue, and depression, and improved quality of life and physical functioning.[12] Two modes of exercise training known as moderate intensity continuous training (MICT) and high intensity interval training (HIIT) have been compared, with the latter prescribed as an important exercise mode and a time-efficient alternative to MICT in enhancing VO2peak and muscle strength and improving fatigue and emotional status in breast cancer patients.[14] Although these types of exercise have been associated with improved functioning and quality of life, clarifying the physiological mechanisms of their effects is important for recommending more efficient and safe exercise programs.

Various physiological mechanisms such as inflammation, hypoxia and angiogenesis are related to breast cancer initiation and development.[15] On the other hand, the effect of exercise on physiological mechanisms such as inflammation and angiogenesis has been investigated[16] which can be common with breast cancer. Thus, the aim of this review is to discuss the potential physiological mechanisms by which exercise may influence breast cancer prevention or treatment. Inflammation and immunity as well as angiogenesis will be emphasized due to their important roles.

METHODS

Search strategy and selection criteria

We reviewed numerous databases for our study during the time frame of 2010 to May 2024. These databases included English articles published in Web of Science, PubMed, Scopus, Cochrane, Embase, Google Scholar, Research Gate, Science Direct, and Persian databases of Magiran and Scientific Information Database (SID). Search keywords included “exercise” or “sport” or “physical exercise” or “high intensity exercise training vs moderate intensity exercise training” and “breast cancer”, “inflammation”, “angiogenesis”,” immune system”, “physiological mechanisms” which had these key terms in their abstracts, keywords, or main bodies. Animal or human studies, original or experimental and review articles were considered. Other cancer types except for breast cancer were excluded.

RESULTS

Overall, papers that focused on the effects of physical activity and exercise on inflammation, immunology, angiogenesis, genetics and other physiological mechanisms were selected. Regarding the main aims of the study, recent papers on inflammation, immunology, and angiogenesis were included for special consideration in human (Table 1) or animal (Table 2) subjects.

DISCUSSION

Exercise, breast cancer, and inflammation

Previous studies indicate that inflammation is important in tumorigenesis. Chronic inflammation can lead to tumorigenesis, through changes in cellular survival, proliferation, transformation, invasion, promotion, angiogenesis, and metastasis.[46] Many extrinsic factors induce inflammation like infections caused by bacteria or viruses, being very overweight, and drinking alcohol which can cause the initiation and progression of cancer. Also, intrinsic variables or cancer-induced inflammation can cause cancer progression.[47]

Various studies have indicated a negative correlation between inflammation and physical activity or exercise.[48] However, there are controversies regarding inflammation and exercise in breast cancer patients or women who are at breast cancer risk. de Jesus Leite et al. [24] found that in post-menopausal women, resistance training increased IL-6 while reduced IL-17.

Table 1. Original studies related to the effect of exercise on inflammatory, immunology, and angiogenesis biomarkers in human subjects (to be continued)

Author	Subjects	Interventions	Biomarkers and results
Jones, *et al.* (2013) [17]	Postmenopausal women	Six months of aerobic exercise.	Women who exercised did not experience any major changes in the markers of inflammation compared to those who did not exercise. Individuals who exercised and attained 80% of the intervention target had less IL-6 than those who did not.
Brenner, *et al.* (2019) [18]	Postmenopausal women with breast cancer.	150 or 300 mins per week of aerobic exercise per year.	Aerobic exercise did not seem to change the levels of VEGF or FGF2 in the blood.
Haley, *et al.* (2020)[19]	Premenopausal women with high risk of breast cancer.	Groups: Control (<75 minutes per week), low-dose exercise (150 minutes per week), or high-dose exercise (300 minutes per week). Home-based treadmill exercise with intensity of 80% of maximum heart rate.	A direct dose-response relationship was for the proinflammatory biomarkers CCL2, IL-12 and TNF-α within the low-dose of exercise, and 15.7% within the high-dose exercise.
Schauer, *et al.* (2021) [20]	Women with breast cancer during chemotherapy.	Exercise for 6 months at high intensity training or low to moderate intensity training during and after their cancer treatment.	No critical difference was found between-group contrasts. Exercise led to critical increments of IL6, IL8, IL10 and TNF post-treatment, but not for IL8. No change was found for CRP or IL1B. CRP and TNF-α increased less with high intensity exercise compared to low to moderate exercise. In patients with breast cancer experiencing chemotherapy, high intensity exercise caused a less increment of CRP and TNF-α compared to low to moderate intensity.
Van Vulpen, *et al.* (2018)[21]	Breast cancer patients during chemotherapy	12-week resistance training or an 18-week combined resistance and high-impact training.	The levels of IL-6, and IL-6/IL-1ra ratio, increased significantly during chemotherapy and decreased afterwards. There was no difference between exercise vs non-exercise groups.
Guinan, *et al.* (2013)[22]	Breast cancer survivors 2-6 months post-chemotherapy.	8-week moderate-intensity aerobic exercise or a usual-care control group.	No difference was found between the exercise and control groups in any of the inflammatory factors.
Dieli-Conwright, *et al.* (2018) [23]	Obese postmenopausal breast cancer survivors	16-week aerobic and resistance exercise (EX) intervention.	The reduction of systemic inflammation, anti-inflammatory cytokines such as adiponectin secreted by adipose tissue, and pro-inflammatory cytokines IL-6 and TNF- α in exercise group.
de Jesus Leite MA, *et al.* (2021) [24]	Postmenopausal breast cancer survivors	12-week resistance exercise and 12 weeks of detraining.	IL-6 increased and IL-17 reduced after resistance and remained lower after detraining.

Table 1. Original studies related to the effect of exercise on inflammatory, immunology, and angiogenesis biomarkers in human subjects (continued)

Author	Subjects	Interventions	Biomarkers and results
Rogers, *et al.* (2013) [25]	Breast cancer survivors	Aerobic moderate-intensity) and resistance exercise.	Non- significant negative impact sizes on IL-10 and proportions of IL-6 to IL-10, IL-8 to IL-10 and TNF-α and TNF-α to IL-10.
Niemiro, *et al.* (2022) [26]	Older women at high-risk of breast cancer	12-week HIIT and MICT	HIIT decreased total granulocytes, CD4 T-cell, CD4 naïve T-cell, recent thymic emigrants and the CD4/CD8 ratio after training. MICT increased total lymphocytes and CD8 effector memory T-cell.
Arana Echarri, *et al.* (2023) [27]	Breast cancer survivors	Laboratory-based treadmill walking and cycling, outdoor walking	Total leukocyte counts, lymphocytes, monocytes and neutrophils did not change with training. Laboratory-based group showed a significant decrease in the CD4/CD8 ratio and significant increase of regulatory NK-cells.
Coletta, *et al.* (2021) [28]	High-risk breast cancer patients	12-week HIIT and MICT	Significant differences were not observed between groups regarding changes in NK-cell function or circulating myokines.
Cannioto, *et al.* (2021) [29]	High-risk breast cancer patients	Physical activity before diagnosis, during treatment, 1 and 2 years after enrollment	Physical activity both before diagnosis and after treatment significantly reduced hazards of recurrence and mortality among breast cancer patients.
Soleimani, *et al.* (2022) [30]	Breast cancer patients	8-week Pilates training (3 days per week)	Pilates training had no significant effect on neutrophil. It had no significant effect on lymphocyte and no effect on the ratio of neutrophil to lymphocyte.
Koivula, *et al.* (2023) [31]	Newly diagnosed breast cancer patients	10-min acute exercise	Total leukocyte count increased immediately after acute exercise (CD8 T-cell, CD19 B-cell, CD56, CD16, NK cells and Cd14, CD16 monocyte).
Khosravi, *et al.* (2021) [32]	Sedentary breast cancer survivors	16-week combined aerobic and resistance training	Exercise training decreased IL-1B, CD14 and CD16. Toll-like receptor 2 and 4 did not change following exercise but decreased 1 h after acute exercise in CD14, CD16 and CD14, CD16 monocyte. Immediately after acute exercise both monocyte subgroup cell concentration increased.
Lee and An (2022) [33]	Female breast cancer survivors	12-week high intensity circuit resistance exercise (HCRE)	HCRE improved BMI, body fat, muscle mass, grip strength, back muscle strength, Y-balance, etc.
Isanejad, *et al.* (2023) [34]	Non metastatic breast cancer patients during adjuvant endocrine therapy	12-week HIIT and MICT	HIIT increased VO2peak compared to MICT and control group. In both groups a significant increase was observed in total functional assessment of cancer therapy. HIIT significantly increased social well-being compared to the control group.
Yeo, *et al.* (2012) [35]	Healthy male college students	High intensity resistance exercise and moderate intensity resistance exercise	VEGF and Ang1 were significantly better in moderate intensity resistance exercise.
Hooshmand Moghadam, *et al.* (2021) [36]	Breast cancer survivors	12-week HIIT and MICT	Both intervention groups significantly decreased body mass, fat mass, TNF-α, IL-6, leptin and increased VO2 peak, lower body strength, upper body strength, IL-10 and adiponectin.

Table 2. Original studies related to the effect of exercise on inflammatory and angiogenesis biomarkers in animal subjects

Author	Subjects	Interventions	Biomarkers and results
Rafiei, *et al.*[37]	BALB/c mice induced breast cancer	Aerobic training for 8 weeks.	Aerobic training did not induce significant changes in VEGF gene expression and reduced angiogenesis.
Jones, *et al.*[38]	Mice fed a high-fat diet implanted with human breast cancer cells	The animals were administered euthanasia as soon as their tumors surpassed 1,500 mm3 in volume.	Oxygen consuming exercise essentially increased intratumoral vascularization.
Rucha, *et al.*[39]	Female Sprague-Dawley rats	Four groups; two N-methyl-N-nitrosourea (MNU)-exposed groups (exercise and inactive) and two control groups (exercise and sedentary).	Exercise increased VEGF- expression and vascularization
Betof, *et al.*[40]	BALB/c mice rats with breast cancer	Aerobic continuous exercise for 8 weeks.	Exercise expanded microvessel size, vessel development and perfusion, and reduced intratumoral hypoxia.
Lee, *et al.* [41]	Breast cancer xenograft mice	Moderate intensity treadmill running for 12 weeks.	Significant reduction in IL-6, IL-18, TNF-α, and CRP mRNA expression levels in exercise group.
Ahmadi *et al.* (2021) [42]	Male Sprague-Dawley rat	8-week HIIT and MICT (5 days per week)	In HIIT group, mRNA levels of MCT4, PGC1- α, HIF1- α were significantly higher than in other groups in soleus muscle.
Shahabpour, *et al.* (2018) [43]	BALB/c mice with induced breast cancer	6-week endurance training (5 days per week)	Endurance training significantly reduced VEGFR-2 in training group compared to control group.
Shalamzari, *et al.* (2024) [44]	BALB/c mice in 4 groups: ETE (exercise-tumor-exercise), ETR (exercise-tumor-rest), RTE (rest-tumor-exercise) and RTR (rest-tumor-rest).	Two groups performed 8-week continuous endurance exercise. Then estrogen-dependent MC4L2 was injected. After that one group performed 6-week endurance exercise	There was a significant reduction in the level of IL-6, VEGF and tumor volume among the groups performing endurance exercise after malignancy (RTE and ETE)
Salehpoor, *et al.* (2023) [45]	Rat model of induced endometriosis	8-week HIIT and MICT and Pentoxifylline medication	HIIT significantly decreased the volume and histological grading of lesion, NFkB, TNF-α and VEGF in lesion. PTX significantly decreased the volume and histological grading of lesion, NFkB and Bcl2, gene expressions of the TNF-α and VEGF in lesions. MICT did not have any significant effect on the variables but HIIT+PTX decreased significantly all of the study variables compared to other interventions.
Bangsub, and Chung (2020)[41]	Breast cancer xenograft mice with or without moderate exercise	12-week moderate intensity physical activity (intensity of 18 m/min), at 30 min for 5 days per week.	IL-6, IL-18, TNF-α, CRP mRNA expression levels of the exercise group significantly decreased compared to those of the no-exercise group and with no difference to the control group.

Also, Haley *et al.*[19] and Dieli-Conwright *et al.*[23] showed a direct negative relationship between inflammatory factors in postmenopausal women. In contrast, Jones *et al.*[17], Rogers LQ *et al.*[25], and Guinan *et al.*[22] found no significant effect of aerobic exercise on inflammation in postmenopausal or breast cancer women. One of the possible reasons for these different findings is the duration of exercise. For example, six or eight weeks of exercise[17,22,25] did not induce significant effects while 12 weeks or a longer duration of exercise[19,23] reduced inflammatory factors significantly.

Some studies assessed the effect of exercise during chemotherapy. Van Vulpen, *et al.*[21] found that there was no difference between exercise vs non-exercise groups regarding inflammatory indices in breast cancer women undergoing chemotherapy. Another study found that in breast cancer patients who were undergoing chemotherapy, high intensity exercise training caused a lower increase in CRP and TNFα immediately after chemotherapy, indicating enhanced protection against chemotherapy-related inflammation.[20] It can be concluded that during chemotherapy, which is associated with inflammation, exercise can suppress inflammation. The stages of treatment can also be effective in acquiring contradictory findings. Some studies found that high intensity exercise may be a more beneficial method of exercise training for the improvement of inflammation, and body composition in breast cancer compared to moderate intensity exercise.[36] A 12-week high intensity circuit resistance exercise was not effective in inflammatory factors.[33] A review study found that exercise training can be recommended to reduce inflammatory factors among the elderly. It is important that acute exercise increases inflammatory factors, while chronic regular exercise training can improve antioxidant mechanisms of the body and reduce inflammatory factors. [49]

Considering the mode of exercise training, there are many challenges regarding the two types of exercise training, i.e., high intensity interval training (HIIT) and moderate intensity interval training (MICT). A study evaluated the effect of a 12-week HIIT and MICT on inflammatory markers in breast cancer survivors and found that compared to the usually-recommended MICT, HIIT may be a more beneficial exercise therapy for the improvement of inflammation.[36] A meta-analysis study including seven randomized trials and 182 patients also showed that regular (3 times per week for 12-16 weeks) HIIT had also a greater tendency than MICT to induce positive effects on inflammation.[50]

Another recent study conducted on the effect of 12 weeks of regular exercise on non-metastatic breast cancer patients during adjuvant endocrine therapy who had been treated with chemotherapy and/or radiotherapy. The study found that there was no significant difference between HIIT and MICT on inflammatory related factors of interleukin-6, tumor necrosis factor-α, or interleukin-10.[34] A recent review compared the effect of HIIT and MICT on obesity indices and found that in the young and middle-aged participants, the effect of HIIT was similar to or better than MICT, while it was influenced by age (18–45 years), complications (obesity), duration (>6 weeks), frequency, and HIIT interval.[51]

Another recent review study also confirmed that HIIT was better than MICT for obesity.[52] Therefore, because inflammation is related to obesity,[53] it is predictable that most probably the same results can be found for inflammatory factors. However, as it was mentioned, most studies approved the positive effects of long term HIIT (>12 weeks), while no study was found regarding the effect of short-term exercise training (<8 weeks). It has been shown that even intense long-term exercise can cause higher levels of inflammatory mediators and chronic inflammation compared to moderate exercise.[54] Thus, although HIIT is recommended for healthy people to reduce inflammation, due to its related short-term inflammation and possible necessary time for anti-inflammatory adaptations of the human body, its recommendation to cancer patients must be interpreted with caution.

In animal models, a study indicated that moderate intensity exercise reduces TNF-*α*, IL-6, IL-18, and CRP expression in mice with breast cancer.[41] Comparing the effects of HIIT and MICT, a study found that in the rat model of induced endometriosis, HIIT was more effective than MICT in reducing inflammatory factors of NF-κB, TNF-α in lesions.[45] There are some controversies which may be related to animal or human subjects of these studies. Specifically, the stage of treatment, intensity and regularity of exercise are very important in determining the effect of exercise on inflammation.

Inflammation can increase chemokines, cytokines, and growth factors which may cause cancer growth. Immune modulation regulates the persistent inflammatory reaction and changes the interference in different signaling pathways such as NF-κB, Nrf-2, JAK-STAT, Akt and MAPKs involved in breast cancer progression.[55] Some proteins like Interleukins, Transforming Growth Factor-β(TGFβ), and TNF-α help cells growth and invasion, metastasis and epithelial–mesenchymal transition in the body.[56] The cellular and immune responses to inflammation prompt the body to repair and regenerate damaged tissue by stimulating cell growth. Therefore, chronic inflammation can cause cell mutation and proliferation, and angiogenesis and create an environment that contributes to cancer.[57]

The anti-inflammatory effect of regular exercise may be attributed to a decrease in visceral fat mass and as a result, a reduction in adipokines, increasing circulatory IL-6 (causing active muscle fibres), IL-10, IL-1 receptor antagonist, and the numbers of IL-10-secreting regulatory T cells. These mechanisms may also include suppressing toll-like receptor expression on monocytes and decreasing downstream responses (e.g., pro-inflammatory cytokine, antigen presentation and co-stimulatory molecule),

circulatory pro-inflammatory monocytes, and suppression of monocyte and macrophage infiltration into adipose tissue.[58] Also, the anti-inflammatory effect of exercise has been attributed to reduced expression and/or activation of pro-inflammatory toll-like receptors (TLRs) in innate immune cells, as the main inflammatory response enhanced by obesity. However, the modulating role of the expression of the toll-like receptors in the reduction of chronic inflammation is not clearly known. [59]

In summary, long term regular exercise training specially HIIT can suppress tumor growth by reducing inflammation which can be due to reduced obesity or/and other physiological mechanisms. However, there is lack of sufficient information considering the effect of different durations and intensities of exercise especially short-term HIIT on inflammation in breast cancer patients.

Exercise, breast cancer, and angiogenesis

Tumor angiogenesis must be considered before the interpretation of mechanisms of exercise impacts on tumor vasculature due to approved effects of exercise on angiogenesis. Angiogenesis causes the growth of cancer because tumors need a blood supply if their size grows more than a few millimeters. The formation and function of the vasculature is determined by pro-angiogenic indices, such as vascular endothelial growth factor (VEGF), and antiangiogenic growth factors.[60] Due to pro-angiogenic factors secreted by tumor cells, tumors can cause proliferation of endothelial cells and the rapid growth of blood vessels as well as the proliferation of endothelial and perivascular cells.[19] In contrast, it has been found that tumor cells can be maintained in severe hypoxia, and increasing tumor hypoxia may increase metastasis.[61] According to recent findings, increased level of angiogenesis is correlated with reduced survival in breast cancer patients.[62] Nevertheless, breast cancer is one of the tumors that has been unable to respond to angiogenesis inhibitors regarding improved survival of patients.[63] Breast cancer cells regulate angiogenesis through releasing pro-angiogenic factors. The hypoxia-inducible factor (HIF) regulates angiogenesis cascade and is an important effective factor in the growth and metastasis of breast cancer.[64]

It seems that aerobic exercise training decreases tumor size and relieves breast cancer by decreasing miR-21 gene expression, and suppressing angiogenesis in BALB/c mice.[37] Jones *et al.*[38] found that in mice fed a high-fat diet implanted with human breast cancer cells, oxygen consuming exercise essentially increased intra-tumoral vascularization. Rucha *et al.*[39] found that in female Sprague-Dawley rats, exercise increased VEGF- expression and vascularization. Betof *et al.* [40] showed that in BALB/c mice rats with breast cancer, exercise expanded microvessel size, vessel development and perfusion, and diminished intratumoral hypoxia. Similarly, another study found that microvessel density within breast tumor models increased after voluntary wheel running in rats.[65] It has been reported that moderate-to-high-intensity treadmill running increases blood perfusion within tumors.[66] Some studies have used markers of angiogenesis. For example, endurance exercise reduced IL-6 secretion which can result in the reduction of the generation of VEGF, causing reduced intra-tumor angiogenesis.[44] Our study indicated that 8 weeks of aerobic exercise increased VEGF while this exercise decreased its receptor in mammary tumor in mice.[43] A study found that in diabetic rats, 8 weeks of MICT was more effective than HIIT in angiogenic factors.[67] Another study compared the effect of HIIT and MICT in the rat model of induced endometriosis on the angiogenic factor of VEGF and found that HIIT was more effective than MICT in reducing VEGF in lesions.[45] Considering the effect of HIIT and MICT, a study evaluated the effects of these two types of training on HIF-1α gene expression in rat skeletal muscle and found that HIIT caused greater positive effects on the gene expression of HIF-1α than MICT.[42] No study was found to compare the effect of exercise with different intensities or durations on angiogenic factors in cancer induced animals.

In human subjects, Brenner *et al.* [18] found that in postmenopausal women with breast cancer, aerobic exercise does not seem to change the levels of VEGF or FGF2 in the blood. Regarding the effect of exercise during chemotherapy on angiogenesis, it has been found that in breast cancer patients who participated in exercise program, the number of CD133+VEGFR2+ circulating endothelial progenitor cells increased over time. Also, 12 weeks of exercise increased placental growth factor (Plgf), a pro-angiogenic factor, and decreased IL-2 in patients.[68] However, regarding the limited number of studies, no comprehensive conclusion can be obtained. HIF-1 has been introduced as a mediating factor in angiogenesis. Findings have indicated that aerobic exercise can reduce hypoxia by improving tumor blood perfusion, resulting in HIF-1 inactivation.[69,70] A study evaluated the effect of resistance exercise with different intensities on blood myokines and angiogenesis in healthy young men, showingthat moderate intensity exercise was more effective than high intensity exercise on myokines (interleukin (IL)-6, IL-8, IL-15) and angiogenesis factors.[35]

Therefore, it seems that different exercise intensities induce various levels of hypoxia. However, similar to animal studies, no study was

found to compare the effect of exercise with different intensities on angiogenic or HIF-1 factors in cancer patients. There are discrepancies regarding the effect of exercise on tumor vasculature which needs more future clarifications.

Exercise, breast cancer, and the immune function

The immune response is important in the process of initiation and progression of cancer. Exercise can cause positive or negative impacts on the immune system which may be due to the duration, intensity, and mode of exercise and depends on the implementation of acute or chronic exercise. In healthy people, it has been shown that exercise increases lymphocytosis, an increase in the number of blood lymphocytes is dependent on exercise intensity.[71] Natural killer (NK) cells are recognized as important factors whose mobilization and activation can be a possible mechanism for the protective impact of exercise on cancer.[72] A review study proposed that increased immunological anti-cancer effects of physical activity are probably through an increase in monocytes, NK cells, and cytokines.[73]

In breast cancer patients, the influence of exercise has been evaluated during and after cancer treatments.[32] The anti-inflammatory effect of combined aerobic and resistance exercise training in breast cancer survivors may be, in part, due to reducing resting monocyte pro-inflammatory cytokine production.[32] The acute or chronic nature of exercise can be importantbecause 30 min acute exercise was reported to increase total leukocyte count, CD8+ T , CD19+ B, CD56+CD16+ NK cell counts immediately.[31] However, eight weeks of pilates exercises did not induce any significant effects on immune factors (neutrophil, lymphocyte , and the ratio of neutrophils to lymphocytes at baseline and following acute exercise) in women with breast cancer.[30] Aerobic exercise and resistance training have exhibited anti-tumor properties through inhibiting tumor growth, reduced metastatic potential and modulation of the tumor microenvironment to allow the recognition and destruction of cancer cells.[74] A systematic review and meta-analysis study assessed the effect of chronic exercise on the immune cells involved in anti-tumor immune responses including natural killers (NK) cells, CD + 4, or CD + 8 and found that exercise did not significantly enhance or suppress the immune system; thus, exercise recommendation must not be discouraged due to immune system cells, but can be recommended considering its benefits for quality of life, physical functioning or fatigue. [75] However, in this review study, the effect of intensity and duration of exercise was not discussed. Another study of 1,340 breast cancer patients indicated that those who met physical activity guidelines (150 min of moderate-intensity physical activity per week) before diagnosis as well as following treatment had a 55% lower risk of recurrence and a 68% lower risk of all-cause mortality.[29]

Although regular moderate exercise results in the reduction of infection compared with a completely sedentary condition, the long duration intensive training performed by elite athletes seems to cause more infections. This is probably due to the fact that anti-inflammatory impacts of exercise causes immunosuppression.[58] A study compared the effect of HIIT and MICT programs on resting NK-cell among women at high risk for breast cancer, reporting that exercise intensity did not affect the fluctuations in resting NK-cell function.[28] However, another study evaluating the effects of 8 weeks of progressively increasing training intensity (55% to 70% V˙O2max) on blood immune cell characteristics among 20 breast cancer survivors Showed that most immune cells were relatively stable during 8 weeks of exercise training among breast cancer survivors. However, the lower counts and activation of CD4+ EMRA T cells might reflect an anti-immunosenescence effect of exercise.[27] This may indicate that increasing the intensity of exercise training may induce suppressive effects on the immune system. Another study evaluated the effect of a 12-week HIIT and MICT on resting NK-cell function and circulating myokines on women at high risk for breast cancer and found that exercise intensity was not effective in resting NK-cell function and circulating myokines and that exercise training induced higher effects on NK-cell function in those with lower levels of cardiorespiratory fitness.[76] However, another study assessed the effects of 12-weeks of HIIT and MICT on the frequency of T-cell subtypes in circulation and their association with circulating levels of the muscle-derived cytokines IL-6, IL-7, and IL-15 in older women at high risk of breast cancer. According to the results, HIIT reduced total granulocytes, CD4+ T-cells, CD4+ naïve T-cells, CD4+ recent thymic emigrants (RTE) and the CD4:CD8 ratio following intervention, whereas MICT increased total lymphocytes and CD8 effector memory (EM) T-cells in human subjects.[26]

In summary, most of the available findings show that aerobic exercise can induce beneficial impacts on NK cell number and function and some other immune functions and cells in cancer patients, while high intensity exercise may induce negative effects. However, there are still limitations regarding the effect of exercise with different intensities and durations. The limited number of study participants and also limited studies indicate that further research is required.

Exercise, breast cancer, and epigenetic gene regulation

"Epigenetics" is the alteration of gene expression without direct altering of the DNA or changing of transcription of the DNA without changing the genetic code. Epigenetic gene regulation has a clear function in the development of cancer.[77] The epigenetic processes such as methylation of DNA, modifications of histone, and noncoding RNAs have been found to be revised by exercise.[78] However, the association between exercise and the epigenetic processes, and its roles in cancer progression, is not completely clear yet.

Methylation can suppress or reduce the expression of some genes, changing cellular function. Exercise may change DNA methylation patterns. Physically active individuals were observed to have higher levels of global DNA methylation compared with inactive people.[79] Studies found that exercise can change gene expression through altering global methylation phenotype or pattern. A study found that physically active women as well as women with an average level of physical activity had higher LINE-1 methylation compared to women with less than median physical activity,[80] indicating that exercise may decrease the risk of cancer initiation and growth partly by improving global methylation levels. Another prospective study evaluated the effect of aerobic exercise on DNA methylation in genes associated with breast cancer, examining whether the quantity of exercise affects changes in DNA methylation in a dose–response manner. The results showed that increased exercise volume and /or fitness may affect methylation of some genes, reducing the risk of breast cancer.[81] Also, there is evidence indicating an association between exercise and histone modifications in immune cell populations in cancer patients, showing that exercise can cause epigenetic alterations. However, a study found non-significant effects of exercise[82] which may be due to the study's design. It is known that MicroRNAs(miRNAs) known as miRs enhance cancer initiation and development through decreasing expression of tumor suppressors or increasing expression of oncogenes.[83] Some findings have indicated a relationship between exercise and miRNA.

In summary, exercise can be proposed as an epigenetic regulator which prevents cancer development, but there is limited evidence that exercise alters miRNA levels relating to cancer development.[84] Therefore, drawing clear conclusions about the relationship between exercise and miRNA expression needs clarification.

Other Mechanisms

Recently, skeletal muscle has been found as an endocrine system that releases numerous growth factors, cytokines (known as myokines), hormones, and other signals.[85] These factors have been involved in tumor development and growth, and can be the target of treatment in various tumor models. Considerable evidence indicates the possibility of mediating role of exercise in muscles/myocytes and tumors/tumor cells.[86,87] A review study showed that myokines may have significant antineoplastic benefits, representing a major mechanism through which exercise affects cancer positively.[88]

Apoptosis can be an important process in eliminating tumor cells growth and development. p53 is an important apoptotic mediator in tumor suppressing process which is inactivated or deleted in several cancer types. Exercise activates p53 in the muscles[89] and may be one of the important protective factors in mechanisms of exercise against cancer. The protective effect of exercise training was found in mammary glands of rats with breast cancer[90] and can be the subject of future studies.

CONCLUSION

The key findings of the present study are as follows: 1) long term regular exercise training specially HIIT can suppress tumor growth probably through reducing inflammation which can be due to reducing obesity or/and other physiological mechanisms, while the effect of short term exercise training is not clear; 2) there are discrepancies regarding the effect of exercise on tumor vasculature which needs more future clarifications; 3) most of the available findings show that aerobic exercise can induce beneficial impacts on NK cell number and function and some other immune functions and cells in cancer patients, while high intensity exercise may induce negative effects; 4) exercise can be proposed as an epigenetic regulator which prevents cancer development; 5) there are still limitations regarding the effects of exercise with different intensities and duration.

According to available findings, regular aerobic exercise can be prescribed for prevention, maintenance and/or recovery of breast cancer. Long-term regular exercise training at the intensity of 55–55% at least twice a week involving main muscle groups can be beneficial in preventing the initiation or progression tumor cells probably through regulating the hemostasis of the body as angiogenesis and inflammation, and preventing harmful effects on the immune system. Considering the effects of the two most common types of training, i.e., HIIT and MICT, although studies have indicated that HIIT was an effective intervention in terms of cardiorespiratory fitness and quality of life in cancer patients and cancer survivors,[91] their physiological effects in breast cancer patients need to be approved. Therefore, for

determining the most proper exercise training mode, intensity, duration and frequency, further research is required to elucidate the specific exercise modalities and mechanisms underlying its effects on breast cancer prevention and treatment.

ETHICAL CONSIDERATIONS

Not applicable.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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DATA AVAILABILITY

All data relevant to the study are included in the article.

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