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The Effect of Different Types of Aerobic Protocols with Different Intensity and Duration on the Management and Recovery of Breast Cancer in Preclinical Studies: A Brief Review

Khosro Jalali-Dehkordi[1], Navid Abedpoor[2]

Short Communication

Abstract

Exercise is effective in preventing and controlling the progression of breast cancer. By inhibiting the growth and metastasis of cancer, physical activity can help manage and delay the side effects caused by cancer and its treatment. It can also increase people's tolerance and adherence to treatment and improve their quality of life. As ethical limitations exist for studying human samples, animal models are suitable for identifying the mechanism of the effect of various diseases in the body and the impact of proposed treatments. Based on these studies, continuous moderate aerobic and intermittent intense exercises, each through different mechanisms, can help prevent cancer, accelerate the treatment process, and reduce and delay complications caused by the disease or its medical and pharmaceutical treatment methods. However, more research is needed to study the molecular mechanisms of the effect of these exercise protocols in greater detail. Finally, research shows that the intensity, duration, and frequency of exercise are important factors that determine the treatment results in cancer control. Therefore, conducting more preclinical and clinical studies in this field is strongly recommended.

Keywords: Medium intensity continuous training; High intensity intermittent training; Breast cancer

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Introduction

Cancer has become one of the most widespread diseases in recent years. In 2018, over 18 million cancer cases were reported in 185 countries worldwide, with 9.6 million resulting in death. Lung cancer remains the most common type, while breast cancer comes in second with a prevalence of 11.6% (11). In Iran, the percentage of cancer incidence and mortality is similar to the global pattern. However, breast cancer tends to affect women in Iran at a younger age than the worldwide average, with the age being reportedly lower by five years (6).

Breast cancer is when abnormal cells grow uncontrollably in various breast tissues, including milk ducts, milk-producing tissue, or non-glandular tissue (3). The common treatments for cancer are surgery, radiation therapy, chemotherapy, immune system-based therapies, and gene therapy. However, these treatments are often associated with toxicity risk and side effects (4).

Paclitaxel is a chemotherapy drug used to treat breast, ovarian, and lung cancer. Unfortunately, this drug cannot be produced from non-chemical sources in sufficient quantities. Paclitaxel works by binding to mitochondrial B-tubulin. This leads to the opening of calcium transport channels, which changes the permeability of the cell membrane to this ion. Consequently, there is an increase in calcium and damage to the mitochondria, leading to cancer cell death through apoptosis and necrosis (5). Paclitaxel has some side effects, including neuro-toxicity, gastritis, nausea, and shortness of breath (6).

Regular and structured physical activity and exercise have been proven effective in preventing breast cancer and increasing the survival rate of people with this cancer. Although scientists have not fully identified the mechanism behind these favorable

1 Associate Professor, Department of Exercise Physiology, School of Physical Education and Sport Sciences, Isfahan (Khorasgan) Branch, Islamic Azad University, Isfahan, Iran
2- PhD Student, Department of Exercise Physiology, School of Physical Education and Sport Sciences, Isfahan (Khorasgan) Branch, Islamic Azad University, Isfahan, Iran
Corresponding Author: Khosro Jalali-Dehkordi, Email: khosrojalali@khuisf.ac.ir

effects, it is highly recommended that an active lifestyle be maintained during and after cancer treatment. Exercise is essential to control and reduce the side effects of cancer treatment. Studies have shown that sports activity can benefit cell proliferation, hormonal response, cell apoptosis rate, and pro-angiogenic and anti-angiogenic events. It can also help predict the behavior of tumors and their metastatic potential and modify these processes. Different sports interventions, such as running on a treadmill, aerobic exercises, and high-intensity interval training (HIIT), have been reported to reduce tumors' incidence, growth, and metastasis.

To identify the biological mechanisms of the effect of exercise and determine the training parameters that bring better results, it is necessary to use animal models to simulate the disease in humans. At the same time, research provides valuable information about tumor physiology. However, preclinical research results are still heterogeneous, probably due to the various exercise protocols used. This prevents experts from agreeing on the strength of the effects of exercise and the type, duration, intensity, and repetition of exercises that have effectively controlled and prevented breast cancer in animals. Therefore, this study aims to investigate the effect of aerobic protocols on breast cancer recovery in preclinical studies.

Moderate Intensity Continuous Training (MICT): Moderate sports activity has positive effects and is generally safe for people with cancer (13, 14). In an animal model of breast cancer in BALB/c mice, moderate-intensity exercise (30 minutes of running on a treadmill at a speed of 18 m/min, five days a week, for 12 weeks) led to the up-regulation of the P53 gene in the tumor tissue. This ultimately reduced tumor growth, likely due to the impact of these exercises on mitochondrial metabolism and micronutrients (15). Similarly, another study showed that moderate-intensity running on a treadmill at a speed of 18 m/min, five days a week for 30 minutes, regulated tumor growth through the responses of immune cells in BALB/c mice with breast cancer (16).

Tumor size and growth are related to the level of interleukin 6 (IL-6), vascular endothelial growth factor (VEGF), and Ki-67 protein (13, 14). An animal model for breast cancer revealed that six weeks of endurance swimming training - if the exercise duration increases from 10 minutes a day with an increase of 8 minutes to 60 minutes a day at the end of the second week - decreased the level of IL-6 and VEGF. This led to a significant decrease in tumor weight and volume. It is worth noting that this effect was intensified by the daily subcutaneous injection of 300 mg/kg of aloe vera extract, while the injection alone did not lead to such results (14).

In the breast cancer model of Sprague Dawley rats, 12 weeks of moderate exercise with a schedule of 5 days per week led to a decrease in tumor cell proliferation and cancer growth (13).

Moderate-intensity aerobic exercise before and after cancer diagnosis helps delay and reduce cancer progression. This is due to the favorable effects of aerobic exercise on chronic systemic inflammation, the acquired immune system's activity, and the hormonal system's change (14, 15). In other words, this type of exercise directly affects the internal factors of the tumor and molecular mechanisms without imposing any side effects. It improves cancer in animal models, and examining these effects in clinical samples is essential to improve the living conditions of people with cancer and health-related indicators.

HIIT: Contrary to popular belief, certain types of intense exercise can positively affect breast cancer tissue. In the meantime, based on new studies in the rat model, participating in HIIT exercises, even for a short period of 4 weeks, can significantly reduce tumor volume by decreasing the expression of the P53 gene (17).

In an extensive study, in a mouse model, the effect of three weeks of daily 60-minute running training at low (speed: six m/s), moderate (10 m/s), and high (15 m/s) intensity with daily intake of Daidzein supplement (a natural isoflavone found exclusively in soybeans and other legumes) at low (45 mg/kg body weight), medium (75 mg/kg body weight), and high (145 mg/kg body weight) doses was compared. In this study, high-intensity exercise and high-dose Daidzein supplementation synergistically reduced tumor growth through redistribution and mobilization of natural killer (NK) cells. This effect was due to the increase of epinephrine and IL-6. Apoptosis of cancer cells was also seen in the group that received both treatments simultaneously, and the final effect was much stronger than the results of using each of these two methods alone (18).

On the other hand, it seems that HIIT improves the number and function of NK cells both in mouse animal models and in obese women with breast cancer. For this reason, it can be considered a potential non-pharmacological strategy for the therapeutic value of this type of exercise (19).

In addition, intermittent aerobic training probably decreases the expression of Vimentin, Twist (20), and B-cell lymphoma 2 (Bcl-2) genes (21). It modifies the expression of the E-cadherin gene, a tumor suppressor gene in mice with breast cancer (22). Therefore, as a

non-pharmacological strategy, it can control tumor invasion, metastasis, and systemic inflammation by modulating gene expression of various suppressors and even reversing disease progression and metastasis (22). However, the simultaneous use of selenium nanoparticles seems to enhance the effect of HIIT training on reducing the Bcl-2 gene (21).

In a study published by Nasiri et al. in 2016, the effect of 60 minutes of running at an intensity of 60%-65% maximal oxygen uptake (VO2 max) as a continuous moderate exercise program with a HIIT program as six 200-second intervals at an intensity of 90%-95% VO2 max, 1 minutes of recovery with an intensity of 30%-35% of VO2 max between each interval, was compared with a regimen of five days a week for ten weeks on ErbB3 gene expression. In both groups, the decrease in ErbB3 expression and thus, in tumor volume was significant. Still, despite the greater reduction in tumor volume in the HIIT group, no significant difference was observed between the two groups (23). Some researchers believe that HIIT reduces tumor volume in mice with breast cancer by lowering pro-angiogenic factors and suppressing the signaling pathways of angiogenesis process (24).

Limitations

This review focuses on laboratory studies carried out in the last five years, which examined the mechanisms of how exercise programs improved breast cancer in animal models. By conducting a systematic review of the mechanisms involved in the effect of exercise programs on this disease, researchers can obtain valuable information to design non-pharmacological clinical treatment programs. However, it is not permissible to use the findings of these studies directly to prescribe exercise to patients with breast cancer.

Recommendations

Conducting a systematic review and quality assessment of existing studies can guide clinical guidelines for exercise prescribing in breast cancer.

Conclusion

Studies have shown that regular moderate aerobic exercise can reduce the blood flow in tumor tissue, decreasing tumor growth. HIIT can help prevent and treat cancer by inhibiting cancer cell multiplication, inducing apoptosis, suppressing angiogenesis, and regulating inflammation. However, more research is required to study the molecular mechanisms of the effects of both MICT and HIIT on cancer cells. While exercise intensity, duration, and frequency play a crucial role in the impact of exercise on tumor volume and growth, conducting more preclinical and clinical studies in this field is highly recommended.

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Authors' Contribution

Study design and ideation: Khosro Jalali Dehkordi, Navid Abedpoor
Attracting financial resources for the study: Khosro Jalali Dehkordi, Navid Abedpoor
Study support, executive and scientific services: Khosro Jalali Dehkordi, Navid Abedpoor
Providing equipment and study samples: Khosro Jalali Dehkordi, Navid Abedpoor
Data collection: Khosro Jalali Dehkordi, Navid Abedpoor
Analysis and interpretation of results: Khosro Jalali Dehkordi, Navid Abedpoor
Specialized statistics services: Khosro Jalali Dehkordi, Navid Abedpoor
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Conflict of Interest

Authors have no conflict of interest.

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