Physical Activity and Hormones (J Physic Act Horm)
Vol. 6 Spring 2025

The Effect of an Incremental Swimming Training Period on CXCR4 Gene Expression in Lung Tissue in a Benzo[a]pyrene-Induced Lung Cancer Model in Balb/c Mice

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ABSTRACT

Introduction: Lung cancer is one of the most lethal malignancies, with smoking and air pollution being its primary risk factors. Early diagnosis and treatment improve survival rates. Studies suggest that inhibiting the CXC motif chemokine receptor type 4 (CXCR4) gene may offer a novel approach to controlling tumor growth and reducing metastasis. This study investigated the effects of incremental swimming training on CXCR4 expression in mice with benzo[a]pyrene (BZP)-induced lung cancer.

Material & Methods: In this experimental study, 12 male Balb/c mice (8–10 weeks old, 18–22 g) were induced with lung cancer via 100 mg/kg BZP injection and divided into two groups: a diseased control group (BZP) and a diseased + exercise group (BZP+ST). Six healthy mice served as the healthy control group (HC). The BZP+ST group underwent a 12-week swimming protocol (3 sessions/week), with durations gradually increasing from 5 to 38 minutes and carrying a load equivalent to 2-5% of their body weight. Data were analyzed using one-way ANOVA and Tukey's post hoc test in SPSS v.22 (significance level: $P \leq 0.05$).

Results: Final body weight was significantly lower in the BZP group compared to HC ($P = 0.001$), but improved in BZP+ST versus BZP ($P = 0.001$). CXCR4 expression was elevated in both BZP and BZP+ST groups compared to HC; however, swimming exercise led to a relative reduction in CXCR4 in the BZP+ST group versus BZP.

Conclusion: Incremental swimming training may suppress tumor growth and metastasis in lung cancer by downregulating CXCR4 expression and improving weight metrics. These findings highlight the potential of physical activity as an effective therapeutic strategy for lung cancer management, warranting further research.

Keywords: Swimming training, CXCR4, Lung cancer, Physical activity.

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Received: Mar 2025; **Revised:** Apr 2025; **Accepted:** May 2025.

DOI: https://doi.org/10.71878/jpah.2025.1205427

1. Introduction

Lung cancer, as a serious and life-threatening disease, is one of the most common cancers worldwide. This condition involves uncontrolled changes in lung cells, leading to the growth of malignant tumors. In many cases, the disease is diagnosed at advanced stages, reducing the chances of effective treatment and patient survival. According to the World Health Organization (WHO) in 2020, approximately 2.21 million new cases of lung cancer were recorded, with nearly 1.8 million deaths attributed to the disease (Javad et al., 2024; Sharma, 2022). These statistics highlight the urgent need for early detection and effective treatment.

Early diagnosis of lung cancer can significantly impact prognosis and treatment outcomes. The highest-risk groups include smokers and individuals exposed to environmental pollutants such as dust and toxic gases. While advances in imaging techniques like CT scans and X-rays aid in early tumor detection, awareness of initial symptoms—such as persistent cough, chest pain, unexplained weight loss, and breathing difficulties—is equally crucial.

Multiple factors contribute to lung cancer development, with smoking being the primary cause, accounting for roughly 85% of cases (Torre et al., 2016). Other risk factors include exposure to environmental carcinogens (e.g., asbestos, radon, and industrial chemicals) and genetic predisposition. Recent studies have identified the chemokine receptor CXC motif chemokine receptor type 4 (CXCR4) as a key player in lung cancer progression. Overexpression of CXCR4 in lung tumors is linked to metastatic processes and poorer prognosis (Zhan et al., 2020). This receptor facilitates cancer cell migration and aggregation (Hattori et al., 2004), and its elevated expression in lung tumor models suggests its potential as a biomarker for disease progression. Targeting CXCR4 may thus offer a novel therapeutic strategy to inhibit metastasis and improve clinical outcomes (Richardson et al., 2013).

Alongside molecular research, physical activity has emerged as a protective factor against cancer and a means to enhance treatment efficacy. Regular exercise positively impacts immune function, reduces inflammation, and improves quality of life in cancer patients (Schmitz et al., 2010). Among various exercises, swimming—a low-impact activity—is particularly recommended for its cardiovascular benefits and minimal strain on the body. Swimming enhances respiratory capacity and muscle strength, alleviating symptoms in cancer patients (Fahlman et al., 2008; Adams et al., 2018). Studies suggest that exercise may modulate cancer-related aberrant phenotypes and promote tissue repair (Brooks et al., 2018), potentially downregulating CXCR4 expression to suppress metastasis (Myers et al., 2018).

This study investigates the effects of an incremental swimming exercise regimen on CXCR4 gene expression in lung tissue using a benzopyrene-induced lung cancer model in Balb/c mice. Balb/c mice are a standard model due to their genetic similarity to humans in immune responses (Gorr et al., 2019), and benzopyrene is a well-established carcinogen for experimental studies (Gonzalez et al., 2013). By exploring the relationship between exercise and cancer-related gene expression, this research aims to provide empirical evidence for integrating physical activity as an adjunct therapy in lung cancer treatment. The ultimate goal is to develop strategies that leverage exercise to modify gene expression (e.g., CXCR4) and mitigate disease progression.

2. Methodology

2.1. Materials and methods

This experimental and fundamental study.

2.2. Participants

This study 18 male Balb/c mice aged 8–10 weeks (weighing 18–22 g) were obtained from the Pasteur Institute of Iran's animal breeding center. After transfer to the animal exercise physiology laboratory at Pishthazan Higher Education Institute of Shiraz, the mice were acclimatized to laboratory conditions for one week. All experimental procedures strictly adhered to ethical guidelines for laboratory animal research and were supervised by the Animal Ethics Committee of Islamic Azad University, Shiraz Branch. Throughout the study, the animals were housed under standard environmental conditions:Temperature: 22 ± 3°C; Humidity: 40–60%; Ventilation: Adequate airflow; Light/dark cycle: 12-hour intervals.

2.3. Measurements

Induction of Lung Cancer with Benzopyrene: To induce lung cancer, 12 laboratory mice were fasted for 12 hours prior to intraperitoneal (IP) injection. Each mouse received 100 mg/kg of benzopyrene (BZP) (Sigma-Aldrich, Product Code: B1760) dissolved in 1.2 mL of corn oil, followed by an IP injection of 10 international units (IU) of the BZP solution (Abekova et al., 2024). Fourteen days post-injection - based on established literature indicating tumor development and inflammation typically manifest within this period - the mice were divided into three experimental groups: After 14 days of injection, based on reliable sources that acknowledge that inflammation and tumor appear during this period, the mice were divided into three groups: healthy control group

(HC), patient control group (BZP), and swimming training group + BZP (BZP + ST). In this study, 6 healthy mice were considered as healthy control group, in order to compare the effects of the experiment on the studied variables.

2.4. Intervention

2.4.1 Swimming training protocol

"In the present study, the swimming exercise was performed with slight modifications based on previous studies. The exercises consisted of 12 weeks of swimming in water maintained at a temperature of 35 ± 1°C. The mice swam in a tub (45 cm width, 80 cm length, and 80 cm height) filled with water to a height of 50 cm. The water level was adjusted so that the mice could not use their tails for support or rest. Swimming sessions were conducted 3 times per week, with each session lasting between 5 to 38 minutes. The swimming duration varied each week over the 12-week period. In the first four weeks, the exercise intensity was limited to swimming without any additional weight. The duration of exercise was 5 minutes in the first week, 8 minutes in the second week, 11 minutes in the third week, 14 minutes in the fourth week, 17 minutes in the fifth week, 20 minutes in the sixth week, 23 minutes in the seventh week, 26 minutes in the eighth week, 29 minutes in the ninth week, 32 minutes in the tenth week, 35 minutes in the eleventh week, and 38 minutes in the twelfth week. To adhere to the principle of progressive overload, no weight was added in the first to fourth weeks. Subsequently, from the fifth to eighth weeks, 2% of body weight was added, and from the ninth to twelfth weeks, 5% of body weight was added. It is worth noting that, considering the variation in the mice's weight and capabilities, the weight attached to their tails was adjusted to match their abilities and ensure appropriate exercise with progressive overload. Following the completion of the exercises, the mice were dried by the trainer using a hairdryer, towel, and suitable room temperature before being returned to their cages (Ramos et al, 2010; Xu et al, 2018; Paceli et al. 2012; Fei et al. 2020).

2.4.2 Dissection, biopsy and weight assessment

Furthermore, 48 hours after the last training session and in a 12-hour fast, the weight of all rats was measured using a digital scale made in Germany, type Kern, with a sensitivity of 0.01 g. Then, the rats were anesthetized using intraperitoneal injection of ketamine at a dose of 25 mg/kg and xylazine at a dose of 65 mg/kg, which is manufactured by Alfasan, Netherlands. After ensuring complete anesthesia, the thoracic cavity of the animals was opened. Then, by removing the connective tissues, the lung tissue was completely extracted. The lung tissue was immediately transferred after washing at a temperature of -70$^{\circ C}$.

2.4.3 CXCR4 measurement method in lung tissue

To measure CXCR4 gene expression levels in lung tissue, RNA extraction was performed using a column RNA extraction kit (FavorPrep™ Tissue Total RNA Kit) with catalog number (FATRK 001) made in Taiwan according to the manufacturer's kit instructions. After RNA extraction, 5 µl of it was placed on an electrophoresis gel to ensure its quality, and its absorption quality was also checked on a Picodrop device made by Sigma-Aldrich, USA, at a wavelength of 260 nm. Then, DNA synthesis was prepared from the extracted RNA using a Fermentase Kit from Thermo Scientific with catalog number (K1621). Also, reverse transcription reaction was performed using the RevertAid First Strand cDNA Synthesis Kit. Next, to examine the CXCR4 gene expression levels using Real-time PCR, all primers (Table 1) were designed using Allele IDv7.8 software, and the Actin Beta (ACTB) gene was used as an internal control. Next, after ensuring the efficiency of the primers, the product was placed in the wells of the Real-time PCR device to amplify the genes in certain time and temperature cycles. After reaching the gene expression threshold cycle (CT), which turns green in the monitor device, the gene expression levels were calculated using the formula 2-ΔΔCt.

Table 1. *Primer sequences of genes used in the research*

Genes	Primer Sequences	Sizes (bp)
TPB	Forward: 5'- GCGGGGTCATGAAATCCAGT-3'	147
	Reverse: 5'- AGTGATGTGGGGACAAAACGA -3'	
CXCR4	Forward: 5'- TTTGGTGCTCCGGTAACCAC -3'	267
	Reverse: 5'- TGTCCGTCATGCTCCTTAGC -3'	

2.5. Statistical Methods

First, the Shapiro-Wilk test was used to check the normality of the data distribution. Then, the paired t-test (dependent) was used to compare the weight changes before and after the intervention. To examine the differences between the groups, the one-way analysis of variance (ANOVA) test was used, and if significant, the Tukey post

hoc test was used to determine the location of the differences. The data were analyzed using SPSS version 22 software. Also, the significance level of all tests was considered to be 0.05 or less ($P \leq 0.05$).

3. Results

The results of the paired t-test showed that the weight of the laboratory mice in the healthy control group in the last week was significantly higher than their weight in the pre-test (P=0.001 and t=-6.84), but in the BZP group, after the intervention, a significant decrease in weight was observed compared to the pre-test (P=0.03 and t=2.81). In contrast, in the swimming training (ST) group, no significant difference was observed between the weight values in the pre-test and post-test (P=0.056 and t=-2.47). Furthermore, the results showed that the post-test body weight values (P=0.001 and F=34.54) were significantly different in the research groups. In other words, the post-test weight in the BZP group was significantly lower than that in the healthy control group (HC) (P=0.001), but in the swimming training group (ST), it was significantly higher than that in the BZP group (P=0.001) (Figure 1).

On the other hand, the results of one-way ANOVA analysis showed that there was a significant difference between the groups at the post-test (P=0.001, F=9 and 2.153). The results of the Tukey post-test showed that the CXCR4 gene expression values in lung tissue in the BZP group (P=0.001) and the BZP+ST group (0.017) were significantly higher than those in the HC group (Figure 2).

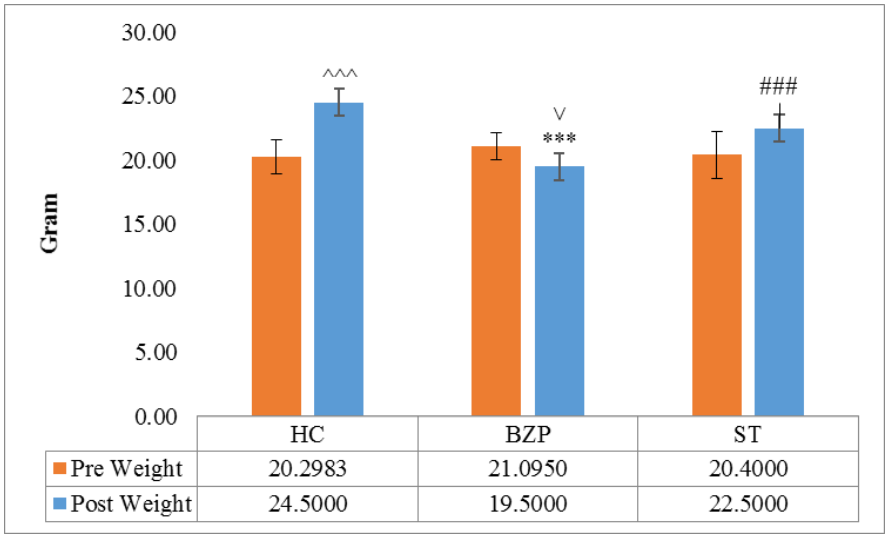
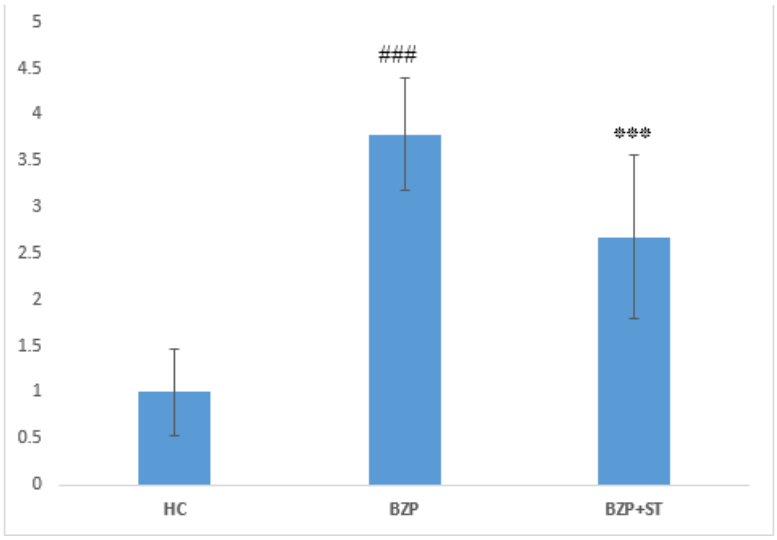


Figure 1. *Weight of laboratory mice in pre-test and post-test in the three research groups. *** (P=0.001) Significant increase in weight in the post-test of the HC group compared to the pre-test of this group; ∨ (P=0.05) Significant decrease in weight in the post-test of the BZP group compared to the pre-test of this group; *** (P=0.001) Significant decrease in weight in the post-test of the BZP group compared to the post-test weight of the HC group; ### (P=0.001) Increase in weight in the post-test of the ST group compared to the post-test of the BZP group*



4.

Figure 2: *CXCR4 gene expression levels in lung tissue in laboratory mice in the three research groups. *** (P=0.001) significant increase compared to the HC group; ### (P=0.017) significant increase compared to the group*

5. Discussion

This study aimed to investigate the effects of incremental swimming training on CXCR4 gene expression in lung tissue and weight indices in a benzopyrene-induced lung cancer model using Balb/c mice. The findings demonstrated that swimming training significantly mitigated cancer-induced body weight loss and downregulated CXCR4 gene expression compared to the cancer control group (BZP).

These results align with previous studies highlighting the role of physical activity in modulating inflammatory and metastatic processes in cancer (Pedersen & Saltin, 2015; Hojman et al., 2011). The observed weight loss in the BZP group is indicative of cancer cachexia, a metabolic syndrome characterized by progressive muscle and adipose tissue wasting (Fearon et al., 2012). Research suggests that activation of inflammatory pathways (e.g., NF-κB) and elevated proinflammatory cytokines (TNF-α, IL-6) play a pivotal role in cachexia development (Argilés et al., 2014).

In contrast, weight stability in the swimming group may be attributed to exercise-induced preservation of muscle mass and improved energy balance. Endurance exercises such as swimming counteract cancer-related catabolism by enhancing muscle protein synthesis and reducing muscle protein degradation via the AKT/mTOR pathway (Hardee et al., 2019).

Research has demonstrated that physical activity enhances insulin sensitivity and regulates visceral fat storage by lowering leptin levels and elevating adiponectin (Stanford & Goodyear, 2014). These effects are likely mediated through the suppression of the JNK/IRS-1 pathway, a key contributor to insulin resistance (Coen & Goodpaster, 2012).

On the other hand, the significant increase in CXCR4 gene expression in the BZP and BZP+ST groups compared to the healthy control group confirms the role of this gene in lung cancer progression. CXCR4 is a chemokine receptor that interacts with its ligand (SDF-1) and facilitates the migration of cancer cells to distant sites (metastasis) (Burger and Kipps, 2006). Clinical studies have shown that high CXCR4 expression is associated with poor prognosis and metastasis to lymph nodes and bones in patients with lung cancer (Spano et al. 2004). The relative decrease in CXCR4 expression in the swimming training group (although still higher than the healthy control group) is probably due to the effect of exercise on signaling pathways related to the transcription factor HIF-1α. Under exercise-induced hypoxia, HIF-1α is activated and inhibits CXCR4 binding by reducing SDF-1 production (Semenza 2012). In addition, exercise may regulate the expression of this gene at the post-transcriptional level by increasing the level of miR-146a, which is a translational inhibitor of CXCR4 (Baggish et al. 2011). Possible mechanisms of exercise's effect on lung cancer include: first Modulation of the immune system: Exercise enhances the antitumor immune response by increasing the activity of NK and cytotoxic T cells (Simpson et al. 2015). second Reduction of oxidative stress: Physical activity reduces DNA damage caused by reactive oxygen species (ROS) by increasing the expression of antioxidant enzymes such as SOD and GPx (Radak 2013). third Regulation of glucose metabolism: Cancer cells are highly dependent on glycolysis for energy and biomass. Excessive production of lactate (the end product of glycolysis under anaerobic conditions) causes the tumor microenvironment to become acidic, which aids cancer cell migration and metastasis. Inhibition of glycolysis has been investigated as a therapeutic strategy in cancer. Therefore, exercise inhibits the growth of cancer cells by reducing lactate levels and the acidity of the tumor microenvironment (Sonveaux et al. 2008). Fourth Effect on intestinal microbiota: Recent studies show that exercise increases butyrate-producing bacteria

that have anti-inflammatory and anti-tumor properties (Mailing et al. 2019). Regarding the limitations of the research, the following can be mentioned: A- Small sample size and use of an animal model limit the generalization of the results to humans. Lack of investigation of other markers associated with metastasis such as MMP-9 and VEGF. Need for long-term studies to evaluate the effect of exercise on patient survival. Therefore, it is suggested that future research should investigate the effect of combining exercise with targeted therapies such as CXCR4 inhibitors (such as Plerixafor). Also, advanced techniques such as RNA sequencing should be used to identify gene networks affected by exercise training.

6. Conclusion

The findings of this study suggest that incremental swimming training—by reducing CXCR4 gene expression and improving metabolic indicators—can serve as a complementary therapeutic approach in lung cancer management. While the exact mechanisms warrant further research, current evidence supports the modulatory role of exercise in influencing the tumor microenvironment and metastatic pathways.

7. Acknowledgment

The researchers hereby thank and appreciate all those who contributed to this research.

Conflict of interests: The authors declare that there is no conflict of interest regarding the publication of this manuscript.

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