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The Impact of Capecitabine and Combined Training on *BRCA1* Gene Expression in Breast Cancer Induction

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A B S T R A C T

Introduction: This study explores the combined effects of concurrent training and capecitabine consumption on breast cancer prevention and therapy, focusing on the modulation of *BRCA1* gene expression.

Material & Methods: In the main study, 12 mice were divided into groups, including Exercise-Tumor-Exercise (ETE), Exercise-Tumor-Exercise+Drug (ETE + D), and various others. Resistance and endurance training were conducted five days a week for 12 weeks before and eight weeks after tumor induction, accompanied by capecitabine administration. *BRCA1* gene expression was assessed post-intervention using SPSS 20.

Results: MC4-L2 injection induced tumors. Both pre and post-cancer induction, exercise significantly increased *BRCA1* gene expression ($p = 0.001$, $p = 0.001$). Exercise combined with post-cancer capecitabine led to increased *BRCA1* expression ($p = 0.001$). Capecitabine alone post-cancer also elevated *BRCA1* expression ($p = 0.001$). Exercise, exercise with capecitabine, and capecitabine alone post-cancer showed significantly higher *BRCA1* expression than exercise pre-cancer ($p = 0.001$). Exercise-tumor-exercise and Exercise-Tumor-Exercise+Drug groups exhibited increased *BRCA1* expression compared to exercise-tumor-drug ($p = 0.001$).

Conclusion: The ETE+D protocol, involving exercise and capecitabine post-cancer, increased BRCA1 expression, suggesting potential roles in tumor prevention and therapy.

Keywords: Breast cancer, Tumor size, Exercise Therapy, *BRCA1*, Capecitabine

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Introduction

Cancer is generally considered a genetic, but not hereditary, disorder that can substantially change the expression of certain genes. In hereditary disorders, genetic defects arise in parental chromosomes and are transmitted to the zygote. On the other hand, the genetic changes associated with cancer occur in somatic DNA throughout life, leading to the uncontrolled proliferation of cancer cells and the formation of malignant masses invading healthy tissues and doubling their growth rate (1). In the case of localized tumors, it is possible to eradicate the malignant mass via surgery, but this strategy is not applicable for metastatic malignant masses in which cells enter the lymph or blood vessels, spreading throughout the body and forming secondary tumors (2). Studies have shown that regular physical activity can have positive effects (the most potent impacts according to some reports) against breast cancer (BC). Exercise can reduce the incidence of secondary diseases in cancer patients. Poor nutrition, depression, anxiety, and poor resting strategies will accelerate cancer progression while adequate exercise under the supervision and approval of a physician can miraculously control and reverse the disease progression (3). Physical activity has been associated with a reduction in the risk of breast, colon, prostate, and lung cancers (4). Researchers believe that regular resistance exercises can reduce the density of neutrophils and macrophages inside the tumor, especially in the early phases of its growth. Inflammatory cells such as macrophages and neutrophils can play two different roles in tumors. On the one hand, they are capable of killing tumor cells, and on the other hand, these cells may accelerate tumor cells' proliferation and growth via producing growth factors and inducing angiogenesis. Although a reduction in inflammatory mediators may not alter tumor size, it will delay tumor growth and, most importantly, tumor regression (5). Exercise usually has a positive effect on most biological processes such as insulin resistance, inflammation, energy expenditure, and the function of most organs. Based on research evidence, physical activity can improve cancer patients' quality of lives, reduce their fatigue, and alleviate many cancer complications during and after the therapeutic course. Therefore, it is important for cancer patients to adhere to exercise protocols and physical activity programs during different stages of the disease (6). Carcinogenesis is a multi-step process intercalated with epigenetic, genetic, and environmental changes. Genetic changes that play a role in this phenomenon affect the pathways involved in cellular growth and trigger the uncontrolled proliferation, growth, and survival of cells. Among these genes are those involved in apoptosis (i.e., programmed cell death), tumor suppressor genes, oncogenes, and DNA repair genes (7). Tumor suppressor genes are important parts of the genome and regulate multiple cellular functions. These genes can be broadly classified based on their roles in the cell (e.g., cell cycle progression, cell proliferation, DNA repair, and other important cellular signaling functions such as apoptosis induction). In the absence of functional tumor suppressor genes, there is a substantial risk for abnormal cell growth,

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which is a known cancer development mechanism (8). In fact, functional mutations in tumor suppressor genes have been identified in many cancers, including ovary, lung, pancreas, uterus, breast, and bladder cancers (9). Various genes have been noted to be involved in BC development, showing different expression levels between cancerous and normal tissues. One of the most important tumor suppressor genes is Breast cancer type 1 (*BRCA1*) that contributes to the repair of double-stranded DNA breaks. Changes in the sequence of the *BRCA1* gene have been reported to increase the risk of a variety of cancers, including BC, and *BRCA1* gene mutations are detected in most BC patients. Mutations in this gene have been reported in approximately 50% and 80% of families with early-onset breast and ovarian cancers, respectively. In women with a family history of BC, the risk of this condition is substantially high, bolding the genetic predisposition of these individuals (10). Around 15% of all BC cases can be related to a strong genetic predisposition, indicating a hereditary pattern. The genes that predispose to hereditary (i.e., familial) BC are classified into high-risk and moderate-risk categories, with *BRCA1* belonging to the high-risk group (11). Both BRCA1 and BRCA2 interact with many proteins and are involved in multiple biological pathways, including DNA repair in which they promote unique roles (12). For example, BRCA1 has a role in the progression of the S and G2 phases of the cell cycle, where it interacts with RAD51. During the repair of double-stranded DNA, the RAD51 protein binds to a single-stranded DNA, forming an adhesive strand that can penetrate into a parallel double-stranded DNA (13). The mechanism by which BRCA1 and BRCA2 promote DNA repair involves integration with DNA homologs and double-stranded DNA breaks. During this process, BRCA2 guides RAD51 towards the DNA damage site by directly binding to this protein. Simultaneously, BRCA1 controls signaling pathways, including those involved in homologous recombination, to ensure that all DNA double-strand breaks are repaired upon RAD51 complex formation (14). Breast cancer type 1 is responsible for repairing damaged DNA repair and also helps destroy cells whose DNA cannot be repaired. If this gene is mutated, DNA repair will not be done properly, boosting the risk of BC. This protein interacts with RNA polymerase II via its C-terminal domain, as well as with the histone deacetylase complex. So, in addition to its role in double-stranded DNA repair, this protein also plays a role in gene transcription. The *BRCA1* gene contains three functional domains, participating in the formation of several protein domains (15). Breast cancer can be treated via surgery, chemotherapy, etc. Various chemotherapeutics involve doxorubicin, capecitabine, etc., which can be prescribed as either injectable or oral form. Capecitabine, a prodrug of 5-fluorouracil, has shown noteworthy antitumor efficacy (16) and is converted into its only active metabolite (i.e., F6) by the thymidine phosphorylase enzyme that is highly expressed in various tumors and the liver tissue compared to normal tissues. Capecitabine has shown acceptable tolerability and varying degrees of efficacy in different cancers, including prostate, kidney, ovary, pancreatic, metastatic breast, and colon cancers (17). Upon oral administration,

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the drug is rapidly absorbed via intestinal-gastric neuronal fibers and converted to 5-fluorouracil (5-FU), its active form, via three enzymatic reactions. Initially, the cytidine deaminase enzyme, which is abundant in the liver and tumor tissue, catalyzes the production of deoxy-5-fluorouridine (5-dFUrd). Finally, 5-dFUrd is converted to 5-FU by the thymidine phosphorylase enzyme, a reaction that exclusively occurs in the tumor tissue (18). The risk of BC has been noted to decrease by leisure familial activities (21% on average), riding a bicycle and walking (18%), and sport competitive activities (13%). Exercise and physical activity at any age can significantly reduce the risk of BC, but the greatest impact of these activities has been reported in the age of 50 years and older. Exercise has been particularly effective in reducing the risk of BC in women without a family history of the disease, postmenopausal women, and women with normal BMIs (19). In a literature review, we found no studies assessing the effect of combined exercises in parallel with capecitabine consumption on BRCA1 gene expression. Therefore, in this study, we aimed to investigate the effects of combined exercises, with or without capecitabine treatment, on BRCA1 gene expression in animal models of BC.

Materials and methods

Experimental Design and Animal Allocation

This true experimental study involved 92 female mice with a mean weight of 15-20 g, obtained from a supplier. The mice were housed in groups of three per cage in a controlled environment with a temperature of 22 ± 2 ºC, relative humidity of 55 ± 5%, and a 12-hour light and dark cycle. Daily measurements of their weight and food intake were recorded throughout the study.

In the primary study, 12 mice were randomly divided into two groups: six healthy mice and six tumor-bearing mice for the induction of breast cancer. Breast cancer was induced experimentally by injecting one million MC4-L2 cancer cells intraperitoneally.

For the main study, 80 mice were randomly assigned to eight groups, each consisting of six mice. The groups were as follows: 1. Exercise-Tumor-Exercise Group (ETE), 2. Exercise-Tumor-Exercise + Drug Group (ETE + D), 3. Exercise-Tumor-Drug Group (ETD), 4. Exercise-Tumor-Rest Group (ETR), 5. Rest-Tumor-Exercise Group (RTE), 6. Rest-Tumor-Exercise + Drug Group (RTE + D), 7. Rest-Tumor-Drug Group (RTD), 8. Rest-Tumor-Rest Group (RTR)

These groups were established to investigate the effects of different interventions on breast cancer in the mice model, considering exercise, drug administration, and rest as variables. The research protocol received approval from the ethics committee of Sistan and Baluchestan University, Zahedan, Sistan and Baluchestan province, Iran, with the ethical code IR.USB.REC.1398.019.

Exercise Training Protocol

In this study, a 12-week combined exercise regimen was implemented, both before tumor development and after the onset of cancer. The exercise sessions were carried out for 8 weeks and comprised a comprehensive protocol

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involving resistance and endurance training.

For the pre-tumor training, animals underwent progressive resistance exercises five sessions per week over 12 weeks. Each session involved four climbing series on a 110-cm vertical ladder inclined at 80º, with a progressively heavier load affixed to the proximal part of the animal's tail using tape. The load for the first two series was set at 50% of the animal's total body mass, progressively increasing to a final load of 100% in subsequent series. The rest interval between series was 60 seconds. A one-week familiarization protocol with the ladder was conducted, involving three trials per day for three days.

The endurance protocol included running exercises on a flat-bed treadmill at a speed of 12 meters per minute. Initially, for 5 days per week and 10 minutes per day in the first week, gradually increasing up to 64 minutes by the 12th week. A one-week running familiarization protocol preceded the main exercises, with speeds ranging from 8 to 10 meters per minute, conducted 5 days per week for 5 to 10 minutes per day.

After tumor formation, an 8-week modified combined exercise routine was implemented. The gavage protocol for the capecitabine drug was as follows: for 8 weeks, every week for 5 days at a rate of 2 mg per week; capecitabine was orally gavaged to mice. Tumor size was measured weekly with a digital caliper.

Tissue Collection

Forty-eight hours after the final training session, the animals underwent anesthesia through intraperitoneal injection of a ketamine-xylazine mixture (30-50 mg/kg ketamine, 3-5 mg/kg xylazine). Tissue samples were extracted from the surrounding areas and immediately preserved in liquid nitrogen at -80 ℃. Homogenization of mouse tissue was carried out in the laboratory. RNA extraction from the homogenized tissues followed the Trizol extraction kit instructions. The expression of the *BRCA1* gene was determined through real-time PCR using a specific kit. Laboratory findings from peripheral tissues were obtained for all eight groups of mice.

RNA and cDNA extraction and purification

Total RNA isolation from peripheral tissue specimens was performed using the Total RNA Extraction Kit (Parstous, Mashhad, Iran). Following traditional deparaffinization with ethanol and xylene solutions, as per the manufacturer's instructions (20), the quantification and quality assessment of total RNAs were conducted using a ScanDrop 250 spectrophotometer (Analytik Jena, Germany) and electrophoresis on a 1% agarose gel, respectively.

To prevent DNA contamination, the total RNA underwent DNase I treatment (Thermo Fisher Scientific, Waltham, MA). Subsequently, the synthesis of first-strand cDNA was carried out using the Easy™ cDNA Synthesis Kit (Parstous, Mashhad, Iran), following the manufacturer's guidelines. The PCR products were then stored at -20 °C for future use.

Quantitative Real-Time PCR for Assessment of BRCA1 Expression Level

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The mRNA expression level of BRCA1 in all 8 groups of mice was assessed by quantitative real-time PCR (qRT-PCR) using the SYBR Green method on a StepOneTM Real-Time PCR System thermocycler (Thermo Fisher Scientific, USA). qRT-PCR reactions followed a thermal cycling profile consisting of 15 s at 95 °C, followed by 40 cycles including denaturation for 30 seconds at 95 °C, annealing for 1 minute at 60 °C, and extension for 30 s at 72 °C. Each experiment was conducted in duplicate tubes and repeated three times on different days. Glyceraldehyde 3-phosphate dehydrogenase (*GAPDH*) served as a reference gene in each experiment. The optimal thermal profile for the studied gene, its primer sequence, and the size of the amplicon and fragment amplified by this primer are presented in Table 1.

Table 1. Primer Sequences and Annealing Temperature for qRT-PCR.

Gene	Sequences (5' to 3')	Annealing Tm (°C)
BRCA1	F- CTGCCGTCCAAATTCAAGAAGT R- CTTGTGCTTCCCTGTAGGCT	60 °C
GAPDH	F- TCAACAGCAACTCCCACTCTTCC R- ACCCTGTTGCTGTAGCCGTATTC	60 °C

Statistical Analyses

SPSS 20 was employed for statistical analysis, and all values were presented as mean and standard deviation. The ANOVA test was utilized to assess significant differences, with a significance level set at $p < 0.05$ for all comparisons.

Results

Based on the results of the Kolmogorov-Smirnov test, all research variables in the research groups exhibited a normal distribution. No significant difference was observed in the body weights among the groups. The study's findings indicated that following MC4-L2 injection, the tumor volume in the induced group exhibited a statistically significant increase compared to the healthy group ($p = 0.001$).

Table 2 reveals a significant difference in *BRCA1* gene expression between the exercise-tumor-rest and rest-tumor-rest groups. Engaging in exercise prior to the onset of breast cancer significantly increased the expression of the *BRCA1* gene in the tumor tissue of female rats.

Table 2. Effect of Exercise Before Breast Cancer on BRCA1 gene expression.

Variable	Groups (each containing 6 rats)	Mean Differences	P- value
BRCA1 Gene Expression	Exercise- Tumor- Rest	1.1400	0.001
	Rest- Tumor- Rest		

According to Table 3, a significant difference in *BRCA1* gene expression is observed between the Rest-Tumor-Exercise and Rest-Tumor-Rest groups.

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Table 3. Effect of Exercise Before Breast Cancer on BRCA1 gene expression.

Variable	Groups (each containing 6 rats)	Mean Differences	P- value
BRCA1 Gene Expression	Rest- Tumor- Exercise	0.890	0.001
	Rest- Tumor- Rest		

As depicted in Table 4, a significant difference in the expression of the *BRCA1* gene is observed between the Rest-Tumor-Exercise+ Drug and Rest-Tumor-Rest groups. Exercise + drug after breast cancer significantly increased the expression of *BRCA1* gene in tumor tissue of female rats.

Table 4. Effect of Exercise + drug After Breast Cancer on *BRCA1* gene expression.

Variable	Groups (each containing 6 rats)	Mean Differences	P- value
BRCA1 Gene Expression	Rest- Tumor- Exercise + Drug	1.680	0.001
	Rest- Tumor- Rest		

According to Table 5, a significant difference in *BRCA1* gene expression is observed between the rest-tumor-drug and rest-tumor-rest groups. Drug after breast cancer significantly increased the expression of *BRCA1* gene in tumor tissue of female rats.

Table 5. Effect of Drug After Breast Cancer on *BRCA1* Gene Expression.

Variable	Groups (each containing 6 rats)	Mean Differences	P- value
BRCA1 Gene Expression	Rest- Tumor- Drug	0.790	0.001
	Rest- Tumor- Rest		

According to Table 6, a significant difference in *BRCA1* gene expression is observed between the Exercise-Tumor-Exercise and Rest-Tumor-Exercise groups. Exercise before breast cancer significantly increased the expression of *BRCA1* gene in tumor tissue of female rats.

Table 6. Effect of Exercise Before Breast Cancer on *BRCA1* Gene Expression.

Variable	Groups (each containing 6 rats)	Mean Differences	P- value
BRCA1 Gene Expression	Exercise- Tumor- Exercise	1.880	0.001
	Rest- Tumor- Exercise		

According to Table 7, there is a significant difference in *BRCA1* gene expression between the Exercise -Tumor-Exercise+Drug and the Rest-Tumor-Exercise+Drug groups. Exercise

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before, along with Exercise+Drug after breast cancer, significantly increased the expression of *BRCA1* gene in tumor tissue of female rats.

Table 7. Effect of Exercise Before along with Exercise+ Drug After Breast Cancer on *BRCA1* Gene Expression.

Variable	Groups (each containing 6 rats)	Mean Differences	P- value
BRCA1 Gene Expression	Exercise- Tumor- Exercise + Drug	1.518	0.001
	Rest- Tumor- Exercise + Drug		

According to Table 8, there is a significant difference in *BRCA1* gene expression between the Exercise-Tumor-Drug and the Rest-Tumor-Drug groups. Exercise before, along with Drug after breast cancer, significantly increased the expression of BRCA1 gene in tumor tissue of female rats.

Table 8. Effect of Exercise Before along with Drug After Breast Cancer on *BRCA1* Gene Expression.

Variable	Groups (each containing 6 rats)	Mean Differences	P- value
BRCA1 Gene Expression	Exercise- Tumor- Drug	1.310	0.001
	Rest- Tumor- Drug		

According to Table 9, when comparing *BRCA1* gene expression between groups following the induction of breast cancer along with pre-induction exercise, the Exercise+ Drug group demonstrated a significantly higher level of *BRCA1* gene expression compared to all other groups.

Table 9. Comparison of *BRCA1* Gene Expression Between Groups After Induction of Breast Cancer along with Pre-Induction Exercise.

Variable	Groups (each containing 6 rats)		Mean Differences	P-value
BRCA1 Gene Expression	Exercise- Tumor- Exercise	Exercise- Tumor- Exercise + Drug	0.42857	0.067
		Exercise - Tumor- Drug	0.70000	0.001
	Exercise - Tumor- Exercise + Drug	Exercise - Tumor- Drug	1.12857	0.001

Discussion

One of the important objectives of this study was to investigate the preventive effects of combined exercises. For this purpose, four groups of mice performed combined (resistance and endurance) exercises for 12 weeks before tumor induction. Combined resistance and endurance exercises have been noted to improve the function of the immune system, cardiovascular system, respiratory system, etc. Research has shown that *BRCA1* gene expression resistance exercise increases the number

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of immune cells, including natural killer cells, in blood circulation and protects the body against infections and tumor development. In addition, *GAPDH* gene expression endurance exercise has been reported to improve the performance of the cardiovascular and respiratory systems, boosting oxygen-carrying ability. In the present research, four groups of mice performed pre-tumor induction exercises (a total of 40 Balb/c mice), 12 of which rejected the tumor. Since all the animals received the same number of cancerous cells (i.e., one million), the rejection of tumors by some of these mice can be attributed to pre-tumor induction activities that strengthened the immune system. Regarding tumor size in the first week, the mice that performed pre-tumor induction exercises (i.e., Exercise-Tumor-Exercise, Exercise-Tumor-Exercise + Drug, Exercise-Tumor-Rest + Drug, and Exercise-Tumor-Rest) showed smaller tumors compared with the animals that did not perform these activities before tumor induction (i.e., Rest-Tumor-Exercise, Rest-Tumor-Exercise + Drug, Rest-Tumor-Rest + Drug, and Rest-Tumor-Rest). Therefore, it can be said that these exercises could promote a type of anti-tumor immunity and prevent tumor growth. Overall, our observations indicated a lower level of tumor growth in the mice that performed combined exercises than the animals that did not perform these exercises. Collectively, regarding the higher tumor rejection rate and the smaller tumor volume observed during the first week after tumor induction in the mice that performed combined exercises, it can be concluded that combined exercises can prevent tumor development or decelerate its growth. According to our results, by changing sedentary machine-oriented lifestyles to more active ones and conducting regular physical activities and sports, it is possible to reduce the risk of *BRCA1* gene expression development. In fact, exercise has a protective effect against *BRCA1* gene expression. People who do regular sports, especially women, are less likely to develop cancer. Also, the risk of developing non-cutaneous cancers has been lower in the women who had performed exercises during their youth than those who did not exercise (21). Research shows that a reduction in sex hormone-binding globulin (SHBG) may increase the risk of *BRCA1* gene expression incidence among women and its recurrence after menopause. In this regard, Liedtke et al. (2011) investigated the relationship between sex hormones and physical activity in postmenopausal women and reported that there was a direct correlation between *GAPDH* gene expression levels and physical activity. However, the relationship between exercise activity and *GAPDH* gene expression levels in postmenopausal women with *BRCA1* gene expression remains unclear (22).

Studies on the effects of exercise on *BRCA1* gene expression are infrequent. It has been suggested that exercise may reduce the risk of BC in the carriers of *BRCA1/2* mutations. Considering the biological role of *BRCA1* and the pathological features of BC, it seems that one of the key functions of this gene is to regulate breast stem cells. It seems that physical activities and exercises can induce substantial biological changes, including changing the number of stem cells (SCs). Regular exercise has been

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reported to affect *BRCA1* gene expression and tumor growth (23). It has been observed that physical activity can reduce the growth of cancerous breast tumors in the adult women carrying a mutant *BRCA1* gene. A 20-day period of treadmill exercises significantly increased the expressions of the *BRCA1*, *p53*, and estrogen receptor-(*ER) β* genes and reduced ER-α in the mammary gland in 14-day-old rats (24). Regarding the inhibitory effect of BRCA1 on estrogen receptors, Zarbaf et al. (2018) reported a decrease in the number of terminal end buds (TEDs) in the mammary glands of the mice born to the mothers who had performed exercise. This was associated with a reduction in ER-β expression (i.e., reduced proliferation) and an increase in the ratio of ER-α to ER-β ratio in mammary lobules and tubes (i.e., a higher rate of differentiation). Overall, these findings correlated with a reduction in the risk of breast tumor development in the siblings whose mothers had performed exercise (25). So far, no study has been conducted on the link between *BRCA1* expression and exercise activities in Balb/c mice with BC. However, tumor suppressor genes, which are important players in preventing gene mutations, have been subjected to many studies. For example, Kazemi et al. (2015) investigated the effect of endurance exercise on the gene expression of microRNA (miR)-155 (an oncogene) and SOCS1 (a tumor suppressor) in the tumor tissues of mice with BC. Their results showed that exercise significantly reduced miR-155 expression and boosted SOCS1 expression in the tumor tissue, suggesting a potential therapeutic role for endurance exercise in BC via enhancing the expression of anti-tumor genes and suppressing the expression of oncogenes (26). Sadeghi Poor Vojdani et al. (2019) conducted a study investigating the impact of intermittent exercise on the gene expression of the E-cadherin tumor suppressor, systemic inflammation, and tumor volume in mice with breast cancer. The findings revealed that intermittent exercise, serving as a non-pharmaceutical approach, effectively influenced the expression of tumor suppressor genes, hindered metastasis, tumor invasion, and systemic inflammation, and even demonstrated the potential to reverse disease progression and metastasis (27). A few studies have been performed on the effect of exercise on *BRCA1* gene expression. Overall, combined exercise seems to be effective in either reducing or delaying tumor growth. The results of the present study revealed that eight weeks of combined exercise (either before or after tumor induction) along with capecitabine treatment decreased the expression of the *BRCA1* gene compared with other groups. These findings suggest that exercise before tumor induction may prevent tumor growth by improving the function of the immune system. The effect of pre-tumor induction exercise was observed to be enhanced after being combined with post-tumor induction exercise and capecitabine treatment, suggesting a synergistic effect between drug consumption and exercise. It seems that combined exercise can modulate stem cells' functions, a feature that is a key function of the *BRCA1* gene as well. More studies are needed to draw accurate conclusions on this subject. Research suggests the contribution of a series of changes in the cancerous transformation of cells. The oncogene triggers cellular proliferation, leading to tumor growth.

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The complex processes that facilitate the growth of cancer cells are not well understood. While we had only a handful of anti-cancer drugs in the past, there are currently multiple chemotherapeutics that travel throughout the body via the bloodstream and eradicate fast-dividing cancerous cells in the body. These drugs may be utilized in a variety of forms (28). During cancer therapeutic course, exercise protocols aim to maintain patients' strength, endurance, and performance so that they recover their previous levels of physical and psychological functions. Aerobic exercise can prevent fatigue, and resistance exercise can help maintain muscle mass. The recent is particularly important as about 50% of people with cancer suffer muscle loss. Chemotherapeutics generally target rapidly-dividing cells, so they can affect healthy dividing cells as well, such as cells in hair follicles, nails, the oral cavity, gastrointestinal tract, bone marrow (i.e., hematopoietic stem cell). Targeted therapies recognize cancer cells' specific features, for example a protein that confers these cells rapid proliferation, and therefore, inflict less harm to healthy cells than chemotherapy drugs. Today, along with the long list of available anti-cancer drugs, other methods such as exercise and physical activity can be used to help eradicate cancer cells or reduce tumor growth. In the therapeutic course of BC, physical activity, in parallel with other medications, can prevent the side effects of chemotherapy and significantly reduce tumor growth. In the present study, we investigated the effect of combined exercises (before and after tumor induction, with or without capecitabine treatment) on tumor growth in mice models of BC. Comparing the two groups of Exercise-Tumor-Drug and Rest-Tumor-Drug at the end of eight weeks of exercise, the results showed a greater reduction in cancer cell growth in the group participating in pre-tumor induction exercise. This observation suggests a role for pre-tumor induction exercise in boosting the function of the immune system. Thus, this exercise protocol can be effective in the treatment of BC, and it is suggested to be used as a complementary strategy along with chemotherapy. The results of the present study showed a higher tumor rejection rate and lower tumor growth in the mice performing combined exercises before and after tumor induction along with capecitabine consumption (i.e., the Exercise-Tumor-Exercise + Drug group) compared to others. Regular exercise can promote psychological and immunological functions, boosting the body's ability to fight against cancerous lesions.

Conclusion

The results of this study showed that the mice that performed pre-tumor induction exercise had better resistance against cancer development. We also compared capecitabine-treated mice that performed post-tumor induction exercise with the animals that received the drug but did not perform the exercise protocol after tumor induction. The results indicated the positive effects of exercise on the cancer chemotherapy course. Therefore, it can be concluded that regular exercise, in addition to a preventive effect, can serve as a complementary approach to reduce the side effects of chemotherapy and help treat estrogen receptor-dependent cancers.

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Conflict of interest

There are no conflicts of interests in the present study.

Authors' contributions

M SN conceived and designed the study, contributed to data acquisition and interpretation, drafted the manuscript. **AS** contributed to the study's conception, interpretation of data, drafted the manuscript. **MB** participated in drafting and critically revising the manuscript. **HF** conceived and designed the study, abstracted and analyzed data.

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