REVIEW

RJME Romanian Journal of Morphology & Embryology http://www.rjme.ro/

# The effect of physical exercises on TNF-*α*, IL-6, and IL-8 cytokines expression and NK cells in cancer

LIGIA RUSU[1)], TATIANA ANDREEA MIHAI[1)], RAMONA ADRIANA SCHENKER[2)], MIHNEA ION MARIN[3)], MICHAEL SCHENKER[4)], COSTIN TEODOR STREBA[5)], DAN IONUŢ GHEONEA[6)], DENISA PIELE[1)]

[1)]*Department of Physiotherapy and Sports Medicine, Faculty of Physical Education and Sport, University of Craiova, Romania*

[2)]*Sf. Nectarie Oncology Center, Craiova, Romania*

[3)]*Department of Applied Mechanics, Faculty of Mechanics, University of Craiova, Romania*

[4)]*Department of Oncology, University of Medicine and Pharmacy of Craiova, Romania*

[5)]*Department of Pulmonology, University of Medicine and Pharmacy of Craiova, Romania*

[6)]*Department of Gastroenterology, Research Center of Gastroenterology and Hepatology, University of Medicine and Pharmacy of Craiova, Romania*

## Abstract

The main process in developing cancer is carcinogenesis, which means that proliferation of the cells is developed and is based on interplay between intrinsic and extrinsic processes. Many researchers consider that cytokines produced during muscle contractions (*i.e.*, myokines) could influence cancer cells. Myokines, produced by muscles during physical activity, may have anti-inflammatory and antitumor effects by directly influencing the tumor microenvironment and the immune system. These signaling molecules have the potential to modulate tumor cell growth and viability, suggesting that exercise may contribute to cancer prevention and control through complex biochemical mechanisms. The aim of this review was to analyze the effects of physical exercise on cytokines and implicitly its influence on the cancer cells, by performing in-depth documentation leading to a synthesis, for analysis of the possible contribution of physical exercises as therapeutic potential. The search for articles was also extended to databases. Multiple studies have shown that exercise can inhibit the development of tumor cells and so apoptosis may be induced for various malignant cells and much more short-term and long-term training interventions suggest that training volume may influence the inhibition of cancer cells. Still, the specific impact of training modalities, volumes, as well as intensities on serum collected from individuals undergoing exercise programs – and its subsequent effects on cancer cells – remains unclear.

***Keywords***: cancer, cytokines, physical exercises, carcinogenesis, myokines.

## Introduction

In 2022, the great number of new cancer patients was 20 million and from these 9.7 million deaths. More than this situation, the survivors up to five years after they receive cancer diagnostic, arise 53.5 million. The statistics speak about the increase in the number of people that develop cancer, so the situation reported in 2022 by the *World Health Organization* (WHO) shows that one in five people develop cancer in their lifetime. Considering these figures and the predicted upward trend for the coming years, cancer is becoming one of the main diseases of interest in medical research.

Cancer develops through a multi-stage process that starts at the cellular level. Cell reproduction is based on a process of cell division. Unlike normal cells, cancer cells ignore signals to stop division, specialization or apoptosis. The main process in developing cancer is carcinogenesis, which means that proliferation of the cells is developed and is based on interplay between intrinsic and extrinsic processes, at the same time increasing the resistance against apoptosis process. Inflammation, although necessary, can influence these processes by promoting neoplasia. Thus, inflammation is considered to be a characteristic that facilitates the acquisition of the major defining features of cancer [1].

In the last years, many studies have been directed towards a number of factors which have been shown to contribute substantially to cancer cell progression and hence tumor masses [2].

Cytokines, defined as signaling proteins produced by different cell types, are produced by immune system components and mediate communication but also in regulating the body's immune and inflammatory responses. They act as chemical messengers, transmitting signals that help coordinate cellular activities such as cell growth, differentiation and migration [3].

However, cytokines act in distinct directions: some cytokines function mainly as growth factors (GFs) for lymphocytes, others have a proinflammatory or anti-inflammatory role, while some cytokines are intended to increase the response to an antigen [4]. Cytokines include chemokines, interferons (IFNs), interleukins (ILs), lymphokines and tumor necrosis factors (TNFs). Each type of cytokine has specific functions, ranging from guiding immune cell migration (chemokines), to stimulating or

inhibiting inflammation (IFNs and TNFs), to modulating immune cell interactions (ILs and lymphokines) [5].

In neoplasms, there are two inflammatory networks: a network including inflammatory mediators which help the antigenic (antitumor) activity, and the second network including antitumor immunity which decreases the level of cumulus of cytokines that supports a chronic, non-specific, pro-tumorigenic inflammation associated with the disruption of normal cell cycle. Between these two networks there is a balance in the tumor stroma, and this will determine the evolution of neoplastic disease [6].

In general, how we know are proinflammatory cytokines that have role in mediate immune interactions for improve the antitumor activity. On the other side are cytokines produced by the environment of the tumor cells, which also sustain carcinogenesis that involve angiogenesis and tumor progression. All these processes are based on a lot of cytokines that participate in carcinogenesis. Many cytokines have two actions because are activate the immune system but also in the development of cancer. At the same time, some cytokines are not enough studied and cannot be used like novel therapeutic targets for reducing the carcinogenesis processes. In this term means that in neoplastic processes development, cytokines are involved on many ways, like increase the carcinogenesis or by their act like anti-tumorigenic roles.

A lot of research describes the role of different cytokines in the body, one of which is IL-6, that is binding to IL-6 receptors. This cytokine plays an essential role in the immune response, being involved in processes such as acute and chronic inflammation, stimulation of protein production in the liver, such as C-reactive protein (CRP), and in regulating cellular response in infections [7]. IL-6 can be as a proinflammatory factor and also could be involved as a GF in various pathological conditions, including cancer and autoimmune diseases [7]. Furthermore, the IL-6 cytokine is involved with the inhibitor processes of apoptotic programs, by producing free radicals. These processes can contribute to the survival of abnormal cells and promote chronic inflammation, having a significant impact in the development of conditions such as tumors and autoimmune disorders. Free radicals have a role in cellular destruction and genomic instability, thus favoring tumor progression [8].

In contrast, IL-2 and IL-12 have also anticarcinogenic roles. The research is done in lung cancer patients, and the results demonstrate that a clinical effect of gene that edited lymphocyte transfer exists. These ILs may stimulate anti-cancer immune responses by activating and proliferating T-lymphocytes and other immune cells, thereby improving the body's ability to fight tumor masses. These approaches have also been tested in advanced cell therapies, demonstrating significant potential in oncology treatments [9].

Regarding tumor necrosis factor-alpha (TNF-$\alpha$), it has two effects like pro and anticancer roles. These roles have been studied in clinical trials regarding genetic therapy. This has anticancer effect of TNF-$\alpha$. This type of therapy has been investigated for its ability to stimulate local immune responses and inhibit tumor growth and has significant potential in innovative oncology treatments [10].

Natural killer (NK) cells are lymphocytes involved in action on the cells that could be dangerous for our body. NK cells recognize and attack abnormal cells without requiring prior sensitization and are thus vital in the early control of cancer and viral infections [11].

However, the category of cytokines is extremely vast and their intervention on the malignant cell is one that requires a broad approach. Even if in curative plans, a series of therapies such as chemotherapy, radiotherapy or immunotherapy maintain their efficacy and durability, currently a minimally invasive approach is being attempted and the development of prophylactic or adjuvant approaches to classical therapies is being developed. An aspect that remains still poorly understood and controversial is the impact that physical activity has on patients diagnosed with cancer, through the effect of modulating cytokine activity in response to coordinated physical activity.

The research papers demonstrate that if the level of physical activity increases, it was observed that this produces a reduction in mortality in colon cancer survivors [12, 13]. This could be explained because of the changes produced by physical and the way is decrease of tumor environment [14, 15]. Exercise may thus help to decrease the possibility of relapses. The main role of physical exercises is to induce the cytokine response and create the anti-carcinogenesis effects [16, 17]. Thus, Pedersen *et al.* (2016) demonstrated that physical exercises have the potential to increase the level of NK cells because they activate the catecholamine mechanisms at the same time with their redistribution *via* IL-6 [16]. By this way, it was observed that there exists a decrease of tumor incidence in a murine model. However, some authors studied NK cells and observed that after physical exercises, the NK cells don't exist and suggests that there is a reduction in tumor cell viability through the catecholamine–cytokine–NK cell mechanism [18]. These results suggest that cytokines released during exercise contribute to antitumor effects through a cellular signaling cascade that promotes an anti-cancerous environment [19]. Many researchers consider that cytokines produced during muscle contractions (*i.e.*, myokines) could influence the cancer cells [15]. Myokines, produced by muscles during physical activity, may have anti-inflammatory and antitumor effects by directly influencing the tumor microenvironment and the immune system. These signaling molecules have the potential to modulate tumor cell growth and viability, suggesting that exercise may contribute to cancer prevention and control through complex biochemical mechanisms.

The impact of physical exercises on the immune system was presented by Koelwyn *et al.* (2015) [20]. They said that in plasma there are exercise-dependent proteomic factors that could have an influence on immune cells. This has a potential direct effect. By this way is possible to prepare the developing of specific phenotypes following their migration and differentiation in tissues [21].

Some studies speak about the possible treatment of cancer based on cytokines, because they could have an important influence in cancer biology in many ways. The role of cytokines we can see regarding the contribution to immunity, cellular destruction, inflammation, angiogenesis. At the same time, tumor microenvironment and molecular biology are under the effects of cytokines. By this way, many authors sustain the effect of cytokines in cancer therapy.

## Aim

The aim of this review was to analyze the effects of

physical exercise on cytokines and implicitly its influence on the cancer cells, by performing in-depth documentation leading to a synthesis, for analysis of the possible contribution of physical exercises as therapeutic potential.

## Study selection for review

This study used thematic analysis, a method often applied in review articles with medical content, emphasizing quality information and a detailed understanding of the topic. One of the search strategies used was the *Setting, Perspective, Intervention, Comparison and Evaluation* (SPICE) method. The documentation was done by consulting specialized journals, and the starting point was the titles and abstracts of the articles published in *PubMed*. We used keywords or combinations of keywords in specific ways to ensure relevance and comprehensiveness of the results by selecting relevant keywords for the search engine, as follows: (*i*) 'cytokine' OR 'interleukin' OR 'myokine' OR 'chemokine'; (*ii*) 'oncology' OR 'cancer' OR 'malignant cells' OR 'neoplastic cells'; (*iii*) 'oncologic physical exercise' OR 'oncologic kinetic intervention' OR 'oncologic kinetotherapy' OR 'oncologic therapeutic program'.

*Inclusion criteria*: studies demonstrating the connection between therapeutic exercise applied to the oncological patient and the impact on cytokine levels were included.

*Exclusion criteria*: studies that did not show results of the involvement of exercise in terms of cytokine influence.

The search for articles was also extended to databases such as *Allied Health Source*, *Cumulative Index of Nursing and Allied Health* (*CINAHL*), *Cochrane*, *EBSCOhost*, *PubMed*, *ProQuest Health & Medical Collection*, *ProQuest Nursing*, *MEDLINE*, *Science Direct* and *SPORTDiscus*.

We considered studies written in both English and French, published in journals and discussing the impact of exercise on oncological diseases, objectified by cytokines.

The *Preferred Reporting Items for Systematic reviews and Meta-Analyses* (PRISMA) diagram in Figure 1 shows how the final pool of articles that formed the basis of this study was selected. We started from a pre-baseline of 278 articles. After the first selection, 188 eligible articles remained. Of these, 113 met all the selection criteria, but 75 articles were eliminated due to content with little impact on the research topic. Seventy-six of these articles were eliminated due to a limited connection existing between cytokine levels and physical activity in oncological diseases, leaving 37 articles from which 13 articles were excluded for not containing pre and post-strength value information.

## Pathophysiological aspects

From the analysis of the 14 selected articles, we have extracted results concerning effects of exercise on cancer cells and on cytokines.

### Effects of exercise on cancer cells

Orange *et al.* (2022) [21] developed a study regarding the stimulation effects of cancer cell line (LoVo) localized in colon on cancer cell proliferation. For this reason, they analyze the serum that was collected before and after an intense physical session and compare with the results to serum collected from a control (no exercise). At the same time, changes of cytokines produced by physical exercise and also changes of intracellular protein expression were analyzed the biological mechanisms involved. Blood samples were obtained from 16 men aged 50 years or older, with lifestyle-related risk factors for colon cancer [body mass index (BMI) ≥25 kg/m$^2$; sedentary lifestyle], both prior to and immediately following the intervention [6×5 minutes intervals at 60% of maximum heart rate ($HR_{max}$)]. The results demonstrate that it is a systemic response after aerobic exercise because the serum marker level indicates that there exists an inhibition cell proliferation for colon cancer *in vitro*, and this effect could be the result of IL-6-induced deoxyribonucleic acid (DNA) regeneration. The mechanism could partly contribute to linking normal physical activity with a decreased risk of colorectal cancer (CRC). Thus, the results suggest that exercise may influence molecular processes that regulate the genetic integrity of cells, with a positive impact on CRC prevention [21].

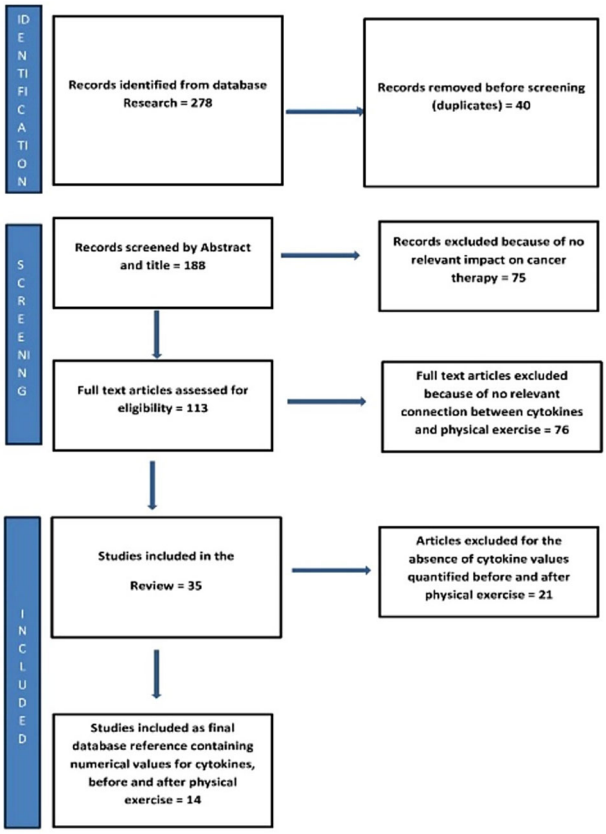


**Figure 1 –** ***PRISMA diagram. PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses.***

Devin *et al.* (2019) [22] conducted a study targeting CRC survivors, such as a high-intensity exercise session that is progressively increased [high-intensity interval exercise (HIIE) of 4×4 minutes at 85–95% of $HR_{max}$]. In the study, serum was collected immediately and 120 minutes after exercise. The effect on growth the cell cancer was assessed through incubation of cells (CaCo-2 and LoVo) for 72 hours and evaluating cell number. The samples' results immediately obtained after the HIIE session, but not at 120 minutes after HIIE, showed an important reduction in the number of neoplastic cells in the colon. Significant increases of IL-6 ($p$=0.023), of IL-8 ($p$=0.036), as well as TNF-$\alpha$ ($p$=0.003) were observed immediately after HIIE [22].

### Effects of exercise on cytokines

Bigley *et al.* (2014) [23] analyzed 16 healthy cyclists who performed three cycling exercise sessions for 30 minutes at intensities of -5%, +5% and +15% relative to lactate threshold. Blood samples collected before, immediately after, and one hour after exercise were used to determine NK cell levels and subtypes, NK cell cytotoxic activity (NKCA), as well as degranulating NK cell subsets [cluster of differentiation (CD)107+] from multiple myeloma (U266 and RPMI-8226), from lymphoma (721.221-AEH and 221-AEH) and from leukemia (K562), using flow cytometry with four and 10 colors, respectively. The results of the study showed that there was an influence of exercise, expressed by an increase of NK cells after an exercise session and one hour after exercise, compared to the value existing before the exercise session. This effect was statistically significant ($p<0.001$). Also, increased exercise intensity was associated with a higher mobilization of NK cells post-exercise and a migration of NK cells at one hour after exercise. Results show that exercise may stimulate the mobilization and migration of NK cells in the blood, which could improve the body's immune response, including against tumor masses [23].

There are studies that have shown that physical exercises' program generated increased chances of survival in breast cancer (BC), but the mechanisms that could reduce the inflammatory process, are not fully understood. Jones *et al.* (2013) [24] looked in this context at changes in IL-6, in CRP and in TNF-$\alpha$ in a study in which an exercise program was presented to postmenopausal BC survivors. A group of 75 women were included in the study; they were recommended either to complete a six-month aerobic exercise program or to care without exercise. Although a relevant effect of physical exercise program on the concentrations of inflammatory marker was not detected in the two groups, subsequent analyses detailed a significant reduction in IL-6 in women who achieved 80% of the aerobic program compared to those who had not reached that goal [24].

In 2013, Rogers *et al.* [25] aimed in their pilot study to determine the magnitude of exercise therapy on serum inflammatory biomarkers and relevant outcomes on the patients' health among BC survivors. Participants were assigned to either the group assigned to physical training over a three-month period or the regular care group. Physical activity was formed by supervised aerobic exercise (moderate intensity, 150 minutes per week) and resistance exercise (two sessions weekly), which were gradually adapted to become home-performed exercises. The evaluation was made at an initial moment and after three months. Although changes in inflammatory markers were relatively low and insignificant, changes followed the hypothesized path for all markers except IL-6 and except IL-10. This trend suggests that although the effects of the intervention were not significant in the short term in terms of reducing inflammation, the observed trends agree with the hypotheses hypothesized, and a stronger effect might be visible in the longer term or with greater adherence to the exercise program. IL-6 and IL-10, as cytokines with an important role in inflammatory processes, may require a specific approach or different conditions to observe significant changes [25].

Glass *et al.*, in 2015 [26], investigated the effects of aerobic exercise on 44 patients with solid tumors, who had received cytotoxic therapy. Significant differences for TNF-$\alpha$ in the group that followed aerobic training (AT) had been noticed [26].

In a study carried out in 2000, Na *et al.* [27] evaluated the impact of exercise on NK cells in patients who underwent surgery for gastric cancer. Thirty-five patients undergoing surgery were randomly split into a control group ($n$=18). and into an exercise group ($n$=17) Starting from postoperative second day, patients performed moderate exercise using an arm ergometer and bicycle twice daily, five days per week for 14 days. Exercise intensity was established at 60% of $HR_{max}$. Samples of venous blood were drawn on the first, the $7^{th}$ and the $14^{th}$ postoperative days. Up until postoperative day 7, the sequential mean modification in NKCA declined; after that, it rose. When compared to the first day following surgery, the mean NKCA for both groups dropped after seven days. On day 14, the exercise group's mean NKCA was significantly higher than that of the control group ($p<0.05$). This study indicates that applying moderate intensity exercise, early, has a specific and important role on *in vitro* NK cell function in patients diagnosed with gastric cancer and after curative surgery [27].

Gómez *et al.*, in 2011 [28], aimed to study the exercise effects on a group of 16 women previously diagnosed with breast neoplasm. The exercise program consisted of eight weeks of exercise (aerobic + strength); at the end of the therapeutic plan, circulating cytokine levels were monitored. Patients were divided as follows: 16 female BC survivors [mean age ± standard deviation (SD): 50±5 years] were assigned to either therapy or a control group. Each group was formed by eight participants. The therapy group completed an exercise protocol of eight weeks organized of three sessions weekly (the duration of each session was 90 minutes), whereas the control group did not complete an exercise program. The primary cytokines associated with BC, for example IL-6 or IL-8, did not significantly decline as a result of the therapeutic regimen. A combined exercise (aerobic + strength) for eight weeks did not produce significant modification in cytokine levels for the survivors of BC [29].

In 2013, Ergun *et al.* [30] conduct a study on a group of 60 patients diagnosed with BC. The patients were distributed into three main groups that followed for a period of three weeks a specific therapeutic program. Group 1 underwent supervised exercise consisting of aerobic and resistive exercise, Group 2 home aerobic exercise, and Group 3 did not follow any rehabilitation protocol involving exercise. At the end of three weeks, the groups were evaluated by monitoring cytokine levels. The levels of IL-6, TNF-$\alpha$, vascular endothelial growth factor (VEGF), growth-related oncogene-alpha (GRO-$\alpha$) upregulated after activation, expressed by normal T-cells, and secreted platelet-derived growth factor (PDGF), thrombopoietin, oncostatin M, monocyte chemotactic protein-2 and -3 did not change significantly after treatment in any of the groups. However, the comparison of IL-8 levels before and after treatment marked a significant decrease for the group of those who performed home exercises [31]. The same IL-8, quantified in a group of 20 patients, cancer survivors, showed equal changes two weeks after performing a moderate intensity exercise program [32].

The statistical analysis performed using XLStat software, of the results obtained included a descriptive and inferential analysis, which aimed to analyze how TNF-α, IL-6, and IL-8 evolve in terms of value after the inclusion of subjects in an exercise program. The results of the statistical analysis for each of the cytokines mentioned above, according to the analyzed studies, are presented in Tables 1–7 and Figures 2–8. Pre and post effort results of statistical analysis are detailed in Table 1 for TNF-α, in Table 3 for IL-6 and in Table 5 for IL-8, while Table 7 details the statistical *t*-test results of cytokine's parameters. The variation of descriptive parameters is detailed for TNF-α in Figure 2, for IL-6 in Figure 4 and for IL-8 in Figure 6. Pearson's correlation is described in Table 2 for TNF-α, in Table 4 for IL-6 and in Table 6 for IL-8, while the regression line is presented in Figure 3 for TNF-α, in Figure 5 for IL-6 and in Figure 7 for IL-8. As a summary, Figure 8 presents the correlation established between physical activity and type of cytokines.

**Table 1** – ***Results of statistical analysis for TNF-α cytokine***

| Author, study year [Ref.] | Pre effort TNF-α cytokine [pg/mL] | Post effort TNF-α cytokine [pg/mL] | Cancer type | Type of exercise | Time of applied protocol |
|---|---|---|---|---|---|
| Rogers *et al.*, 2013 [25] | 9.60 | 7.00 | BC | MIIE and resistance | Three months, 150 minutes weekly, two times/week |
| Glass *et al.*, 2015 [26] | 1.00 | 1.00 | Solid tumors | Aerobic training | 30–45 minutes/session for 12 weeks |
| Bower *et al.*, 2014 [29] | 7.70 | 8.50 | BC | Yoga intervention | 12 weeks |
| Jones *et al.*, 2012 [33] | 1.15 | 1.17 | BC | MIIE aerobic | 150 minutes/week, six months |
| Jones *et al.*, 2013 [24] | 0.15 | 1.17 | BC | MIIE aerobic | 150 minutes of moderate intensity |
| Gómez *et al.*, 2011 [28] | 27 | 22 | BC | Aerobic + strength exercises | Eight weeks, three sessions/week, 90 minutes/session |
| Ergun *et al.*, 2013 [30] | 13.01 | 11.6 | BC | MIIE aerobic and resistance exercises | 45 minutes/day for three days/week, walking 30 minutes/day for three days/week |
| Minimum value | 0.150 | 1.000 | | | |
| Maximum value | 27.000 | 22.000 | | | |
| Mean value | 8.516 | 7.491 | | | |
| SD | 9.526 | 7.645 | | | |

BC: Breast cancer; MIIE: Moderate-intensity interval exercise; SD: Standard deviation; TNF-α: Tumor necrosis factor-alpha.

**Table 2** – ***Pearson's correlation for TNF-α cytokine, between pre and post effort measurement***

| Variables | Pre effort TNF-α cytokine | Post effort TNF-α cytokine |
|---|---|---|
| Pre effort TNF-α cytokine | 1 | 0.992 |
| Post effort TNF-α cytokine | 0.992 | 1 |

TNF-α: Tumor necrosis factor-alpha. We observe a high correlation before and after effort.

**Table 3** – ***Results of statistical analysis for IL-6 cytokine***

| Author, study year [Ref.] | Pre effort IL-6 cytokine [pg/mL] | Post effort IL-6 cytokine [pg/mL] | Cancer type | Type of exercise | Time of applied protocol |
|---|---|---|---|---|---|
| Orange *et al.*, 2022 [21] | 24.60 | 37.90 | Colon cancer | MIIE | ≥30 minutes moderate to HIIE, ≥3 days/week, three months |
| Rogers *et al.*, 2013 [25] | 19.70 | 23.60 | BC | MIIE and resistance | Three months, 150 minutes weekly, two times/week |
| Gómez *et al.*, 2011 [28] | 16.30 | 11.80 | BC | MIIE and resistance | Eight weeks, three times/week |
| Ergun *et al.*, 2013 [30] | 3.30 | 2.89 | BC | MIIE and resistance | Twelve weeks, three times/week |
| Bower *et al.*, 2014 [29] | 1.34 | 1.64 | BC | Yoga intervention | 12 weeks |
| Rogers *et al.*, 2013 [25] | 2.60 | 2.80 | BC | MIIE aerobic | Three-month exercise intervention (160 minutes/week) |
| Jones *et al.*, 2012 [33] | 3.5 | 3.59 | BC | MIIE aerobic | 150 minutes/week, six months |
| Orange *et al.*, 2022 [21] | 0.5 | 0.68 | Colon cancer | Moderate-intensity aerobic | 30 minutes, three days/week, three months |
| Jones *et al.*, 2013 [24] | 3.55 | 3.59 | BC | Moderate intensity | 150 minutes/week, three session/week |
| Gómez *et al.*, 2011 [28] | 26 | 21 | BC | Aerobic + strength exercises | Eight weeks, three sessions/week, 90 minutes/session |
| Ergun *et al.*, 2013 [30] | 2.9 | 2.97 | BC | MIIE aerobic + resistance | Forty-five minutes/day, three days/week, walking 30 minutes/day, three days/week |

| Author, study year [Ref.] | Pre effort IL-6 cytokine [pg/mL] | Post effort IL-6 cytokine [pg/mL] | Cancer type | Type of exercise | Time of applied protocol |
|---|---|---|---|---|---|
| Minimum value | 0.500 | 0.680 | | | |
| Maximum value | 26.000 | 37.900 | | | |
| Mean value | 9.481 | 10.224 | | | |
| SD | 9.996 | 12.156 | | | |

BC: Breast cancer; HIIE: High-intensity interval exercise; IL-6: Interleukin-6; MIIE: Moderate-intensity interval exercise; SD: Standard deviation.

**Table 4** – ***Pearson's correlation for IL-6 cytokine, between pre and post effort measurement***

| Variables | Pre effort IL-6 cytokine | Post effort IL-6 cytokine |
|---|---|---|
| Pre effort IL-6 cytokine | 1 | 0.924 |
| Post effort IL-6 cytokine | 0.924 | 1 |

IL-6: Interleukin-6. We observe a high correlation before and after effort.

**Table 5** – ***Results of statistical analysis for IL-8 cytokine***

| Author, study year [Ref.] | Pre effort IL-8 cytokine [pg/mL] | Post effort IL-8 cytokine [pg/mL] | Cancer type | Type of exercise | Time of applied protocol |
|---|---|---|---|---|---|
| Rogers *et al.*, 2013 [25] | 7.30 | 6.70 | BC | MIIE and resistance | Three months, 150 minutes weekly, two times/week |
| Gómez *et al.*, 2011 [28] | 20.20 | 21.20 | BC | Aerobic and resistance | Eight weeks, three sessions/week, 90 minutes/session |
| Ergun *et al.*, 2013 [30] | 10.37 | 7.76 | BC | Aerobic and resistance | Twelve weeks, three times/week |
| Rogers *et al.*, 2013 [25] | 6.8 | 5.4 | BC | MIIE aerobic | Three-month exercise intervention (160 minutes/week) |
| Gómez *et al.*, 2011 [28] | 27 | 22 | Colon cancer | Aerobic exercise | Eight weeks, three sessions/week, 90 minutes/session |
| Minimum value | 6.800 | 5.400 | | | |
| Maximum value | 27.000 | 22.000 | | | |
| Mean value | 14.334 | 12.612 | | | |
| SD | 8.899 | 8.252 | | | |

BC: Breast cancer; IL-8: Interleukin-8; MIIE: Moderate-intensity interval exercise; SD: Standard deviation.

**Table 6** – ***Pearson's correlation for IL-8 cytokine, between pre and post effort measurement***

| Variables | Pre effort IL-8 cytokine | Post effort IL-8 cytokine |
|---|---|---|
| Pre effort IL-8 cytokine | 1 | 0.968 |
| Post effort IL-8 cytokine | 0.968 | 1 |

IL-8: Interleukin-8. We observe a high correlation before and after effort.

**Table 7** – ***Statistical t-test results of cytokines' parameters***

| Parameters | TNF-α cytokine | IL-6 cytokine | IL-8 cytokine |
|---|---|---|---|
| Difference | 1.024 | -0.743 | 1.722 |
| *p** | 0.257 | 0.620 | 0.163 |

IL-6: Interleukin-6; IL-8: Interleukin-8; TNF-α: Tumor necrosis factor-alpha. **p*-value two-tailed; significance level α=0.07. We observe that there is not a significant statistical difference of cytokines level pre and post effort.

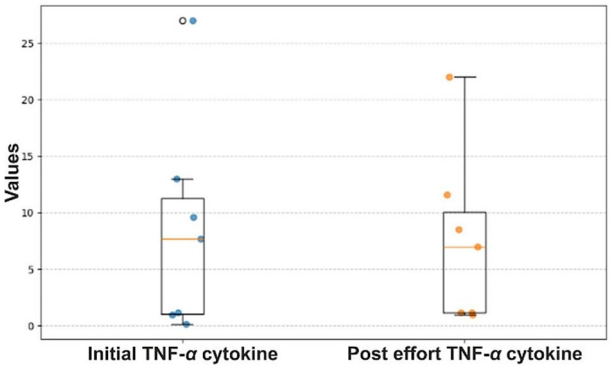


**Figure 2** – ***Variation of descriptive parameters for TNF-α cytokine, pre and post effort. TNF-α: Tumor necrosis factor-alpha.***

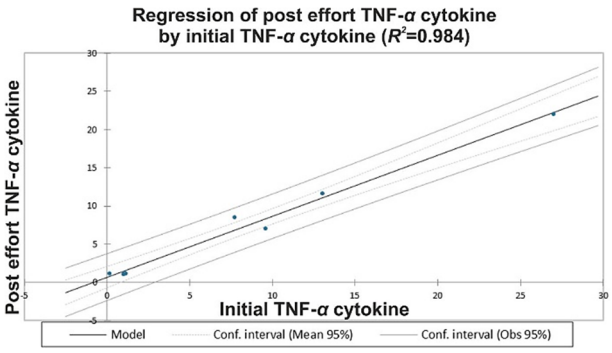


**Figure 3** – ***Regression line of TNF-α cytokine, pre and post effort. This could be considered a prognosis about the evolution of TNF-α.***

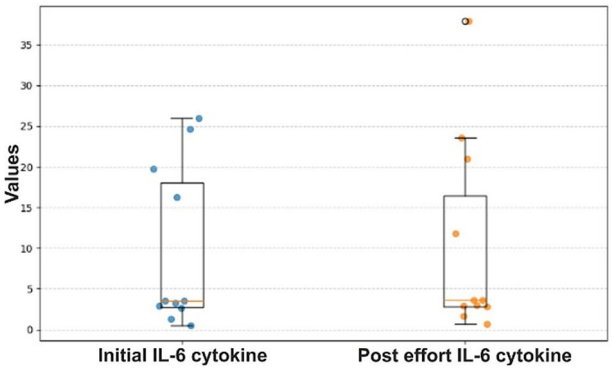


**Figure 4** – ***Variation of descriptive parameters for IL-6 cytokine, pre and post effort. IL-6: Interleukin-6.***

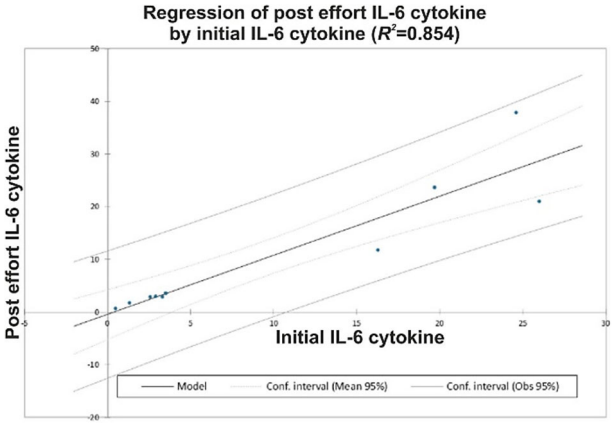


**Figure 5** – ***Regression line of IL-6 cytokine, pre and post effort. This could be considered a prognosis about the evolution of IL-6.***

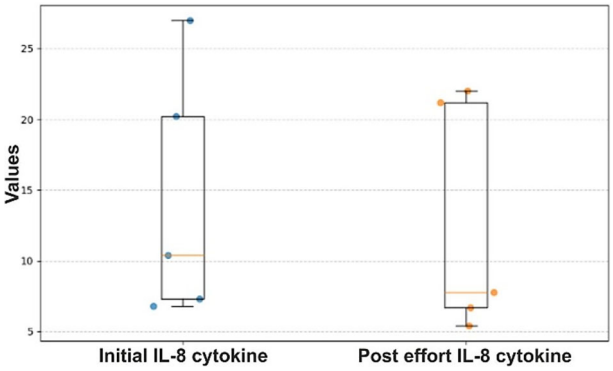


**Figure 6** – ***Variation of descriptive parameters for IL-8 cytokine, pre and post effort. IL-8: Interleukin-6.***

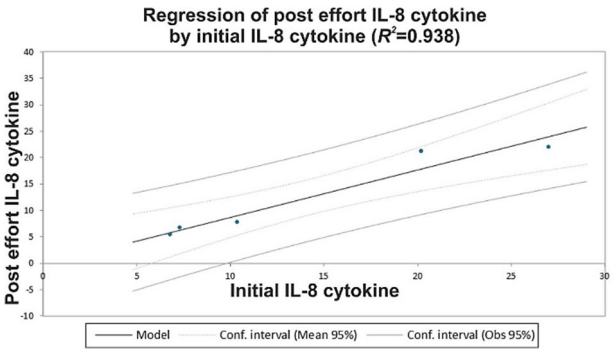


**Figure 7** – ***Regression line of IL-8 cytokine, pre and post effort.***

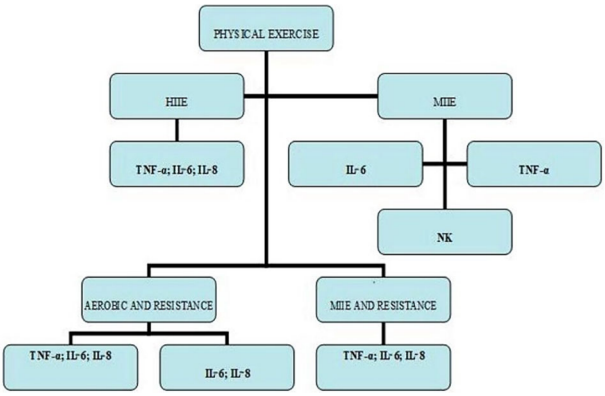


**Figure 8** – ***Correlation between physical activity and type of cytokines. HIIE: High-intensity interval exercise; IL-6: Interleukin-6; IL-8: Interleukin-8; MIIE: Moderate-intensity interval exercise; NK: Natural killer; TNF-α: Tumor necrosis factor-alpha.***

IL-6 is the cytokine produced by skeletal muscle, and it is responsible for increasing the circulating level of cytokines that play an anti-inflammatory role, such as IL-1Ra or IL-10. Physical exercise programs could be structured as aerobic exercise, or can be shaped as resistance exercise, can gather both the aerobic and the resistance exercise, as well as yoga. Different forms of intensity can be applied like moderate or moderate-vigorous, as well as only vigorous. The period may vary between six and up to 24 weeks. The duration of each session may also vary between 15 to 90 minutes. Sessions can also be supervised, home-based, or combined.

Although as shown in many studies, exercise did not alter other serum markers, it is improbable that the growth-inhibitory tendency of exercise was exclusively attributed to IL-6. The main anti-cancer effects are because in the acute phase of physical exercise the level of IL-6 increases but the continuation of training has as an ultimate result a decrease of resting IL-6 value. The complementary role of IL-6 suggests that contrasting systemic responses to either acute or chronic exercise may each play a part in suppressing cancer progression.

## Discussions

Although the relationship between physical therapy and immune biomarkers exists, the subject continues to draw attention of researchers and clinicians.

The present research underlines the direct impact of regular exercise on serum concentrations and its contribution to decreasing some proinflammatory mediators, such as IL-6, in cancer survivors. Findings as the above mentioned were reported in 2012 by Loef & Walach [34]. The research supports low to moderate evidence that interventions involving physical exercise impact serum biomarker levels.

The number as well as the functionality of varied types of immune cells, with essential role in fighting cancer, has been proven to be improved by physical activity. For instance, physical exercise enhances both the activity as well as the number of NK cells, of dendritic and T-cells, all playing crucial roles in identifying and eliminating malignant cells [33].

Studies have demonstrated that IL-6 induced by exercise

possesses direct and indirect anti-cancer effects. For instance, the serum obtained from men with lifestyle-related risk factors immediately after moderate-intensity aerobic exercise significantly inhibited the multiplication of CRC cells. This suggests a strong suppressive effect of IL-6 on CRC cells. The inhibition of CRC cell proliferation through exercise may partly result from IL-6's influence on DNA damage and repair mechanisms.

A topic of interest in the continuation of this study remains the type of physical activity indicated.

The immunological benefits of an exercise program can be maximized by tailoring its intensity, duration, and type to each patient's unique demands. The design of therapeutic programs should consider factors including the type of cancer, treatment stage, general health, and genetic profile. For example, moderate-intensity aerobic exercise, which has been demonstrated to enhance tumor blood flow and oxygenation, may benefit patients with solid tumors more, hereby enhancing the efficacy of treatments like chemotherapy and radiation therapy [35].

A long-term exercise program refers to a structured regimen performed consistently over an extended period, typically involving two or more sessions per week for a minimum period of 8–12 weeks. In contrast, a period of 2–8 weeks is considered a short-term program. Specific training is outlined in current standards for cancer survivors. Criteria for AT and resistance training (RT), such as suggested volume (*e.g.*, minutes) and intensity (*e.g.*, sets and repetitions) are considered.

These guidelines also emphasize the importance of specific frequencies and durations to achieve desired physical and physiological adaptations [36].

From a physiological perspective, interventions of an exercise program over a long duration of time may also influence circulating factors. In fact, as seen, in our selected studies, it was proven that for survivors of BC, physical exercise conducted over a period of six to 48 weeks, which was organized in 2–3 sessions each week, had positively modified levels of insulin, IL-6 and insulin-like growth factor-1 (IGF-1), as well as different biomarkers of the inflammatory process [37].

Dethlefsen *et al.* [17] studied the impact of a 90-minute weekly program combining RT and high-intensity interval training (HIIT) over six months, and compared the results of a control group, to a 74 BC group. When serum collected from the exercise group was applied to BC-specific cells (MCF-7 and MDA-MB-231) *in vitro*, there was no observed effect on cancer cell viability. Additionally, significant changes were noted only for IL-6 and for TNF-$\alpha$ levels, while the majority of markers, such as insulin IL-8, or IL-10, remained unchanged [17]. These aspects are important and support the results presented in the studies reviewed in this paper.

Conversely, increasing evidence highlights the link created between reduced physical activity, inflammation, and progression of malignant cells, underscoring the detrimental effects of sedentary behavior on hormone levels, cytokines, and inflammation. This indicates that higher levels of physical activity might indirectly contribute to a decrease in systemic proinflammatory cytokines [13].

## Conclusions

Over the past two decades, the potential anti-cancer and tumor mass-sparing benefits of exercise have gained significant attention. Multiple studies have shown that exercise can inhibit the development of tumor cells and so apoptosis may be induced for various malignant cells. Still, the specific impact of training modalities, volumes, as well as intensities on serum collected from individuals undergoing exercise programs – and its subsequent effects on cancer cells – remains unclear. The reduced research in this emerging area of oncology limits the ability to draw generalized conclusions. Nonetheless, existing findings indicate that one session of moderate to vigorous intensity exercise might exert suppressive effects on cancer cells and significantly elevate circulating factors. Evidence from both short-term and long-term training interventions suggests that training volume may influence the inhibition of cancer cells and the modulation of circulating factors, independent of the type of exercise performed. Future studies should focus on the effects of exercise on malignant cells by examining specific training modalities (*e.g.*, resistance *vs*. aerobic exercise), as well as variations in volume and intensity. Such research should aim to uncover the mechanisms behind exercise-induced cancer suppression and changes in circulating biomarkers, while also accounting for factors like muscle mass and alterations in body composition caused by the disease and its treatments.

### Conflict of interests

The authors declare no conflict of interests.

## References

[1] West NR, McCuaig S, Franchini F, Powrie F. Emerging cytokine networks in colorectal cancer. Nat Rev Immunol, 2015, 15(10): 615–629. https://doi.org/10.1038/nri3896 PMID: 26358393

[2] Peddareddigari VG, Wang D, Dubois RN. The tumor microenvironment in colorectal carcinogenesis. Cancer Microenviron, 2010, 3(1):149–166. https://doi.org/10.1007/s12307-010-0038-3 PMID: 21209781 PMCID: PMC2990487

[3] Zhang JM, An J. Cytokines, inflammation, and pain. Int Anesthesiol Clin, 2007, 45(2):27–37. https://doi.org/10.1097/AIA.0b013e318034194e PMID: 17426506 PMCID: PMC2785020

[4] Dinarello CA. Historical insights into cytokines. Eur J Immunol, 2007, 37(Suppl 1):S34–S45. https://doi.org/10.1002/eji.200737772 PMID: 17972343 PMCID: PMC3140102

[5] García Morán GA, Parra-Medina R, Cardona AG, Quintero-Ronderos P, Rodríguez ÉG. Chapter 9: Cytokines, chemokines and growth factors. In: Anaya JM, Shoenfeld Y, Rojas-Villarraga A, Levy RA, Cervera R (eds). Autoimmunity: from bench to bedside [Internet]. El Rosario University Press, Bogota, Colombia, 2013 Jul 18. https://www.ncbi.nlm.nih.gov/books/NBK459450/

[6] Mager LF, Wasmer MH, Rau TT, Krebs P. Cytokine-induced modulation of colorectal cancer. Front Oncol, 2016, 6:96. https://doi.org/10.3389/fonc.2016.00096 PMID: 27148488 PMCID: PMC4835502

[7] Moulton VR. Chapter 17 – Cytokines. In: Tsokos GC (ed). Systemic lupus erythematosus: basic, applied and clinical aspects. Academic Press–Elsevier, London, UK, 2016, 137–141. https://doi.org/10.1016/B978-0-12-801917-7.00017-6

[8] Heichler C, Scheibe K, Schmied A, Geppert CI, Schmid B, Wirtz S, Thoma OM, Kramer V, Waldner MJ, Büttner C, Farin HF, Pešić M, Knieling F, Merkel S, Grüneboom A, Gunzer M, Grützmann R, Rose-John S, Koralov SB, Kollias G, Vieth M, Hartmann A, Greten FR, Neurath MF, Neufert C. STAT3 activation through IL-6/IL-11 in cancer-associated fibroblasts

promotes colorectal tumour development and correlates with poor prognosis. Gut, 2020, 69(7):1269–1282. https://doi.org/10.1136/gutjnl-2019-319200 PMID: 31685519

[9] Chiocca EA, Yu JS, Lukas RV, Solomon IH, Ligon KL, Nakashima H, Triggs DA, Reardon DA, Wen P, Stopa BM, Naik A, Rudnick J, Hu JL, Kumthekar P, Yamini B, Buck JY, Demars N, Barrett JA, Gelb AB, Zhou J, Lebel F, Cooper LJN. Regulatable interleukin-12 gene therapy in patients with recurrent high-grade glioma: results of a Phase 1 trial. Sci Transl Med, 2019, 11(505):eaaw5680. https://doi.org/10.1126/scitranslmed.aaw5680 PMID: 31413142 PMCID: PMC7286430

[10] Chang KJ, Reid T, Senzer N, Swisher S, Pinto H, Hanna N, Chak A, Soetikno R. Phase I evaluation of TNFerade biologic plus chemoradiotherapy before esophagectomy for locally advanced resectable esophageal cancer. Gastrointest Endosc, 2012, 75(6):1139–1146.e2. https://doi.org/10.1016/j.gie.2012.01.042 PMID: 22520270 PMCID: PMC4543382

[11] Chiossone L, Dumas PY, Vienne M, Vivier E. Natural killer cells and other innate lymphoid cells in cancer. Nat Rev Immunol, 2018, 18(11):671–688. https://doi.org/10.1038/s41577-018-0061-z. Erratum in: Nat Rev Immunol, 2018, 18(11):726. https://doi.org/10.1038/s41577-018-0077-4 PMID: 30209347

[12] Meyerhardt JA, Giovannucci EL, Holmes MD, Chan AT, Chan JA, Colditz GA, Fuchs CS. Physical activity and survival after colorectal cancer diagnosis. J Clin Oncol, 2006, 24(22):3527–3534. https://doi.org/10.1200/JCO.2006.06.0855 PMID: 16822844

[13] Friedenreich CM, Ryder-Burbidge C, McNeil J. Physical activity, obesity and sedentary behavior in cancer etiology: epidemiologic evidence and biologic mechanisms. Mol Oncol, 2021, 15(3):790–800. https://doi.org/10.1002/1878-0261.12772 PMID: 32741068 PMCID: PMC7931121

[14] Betof AS, Dewhirst MW, Jones LW. Effects and potential mechanisms of exercise training on cancer progression: a translational perspective. Brain Behav Immun, 2013, 30(Suppl):S75–S87. https://doi.org/10.1016/j.bbi.2012.05.001 PMID: 22610066 PMCID: PMC3638811

[15] Idorn M, Hojman P. Exercise-dependent regulation of NK cells in cancer protection. Trends Mol Med, 2016, 22(7):565–577. https://doi.org/10.1016/j.molmed.2016.05.007 PMID: 27262760

[16] Pedersen L, Idorn M, Olofsson GH, Lauenborg B, Nookaew I, Hansen RH, Johannesen HH, Becker JC, Pedersen KS, Dethlefsen C, Nielsen J, Gehl J, Pedersen BK, Thor Straten P, Hojman P. Voluntary running suppresses tumor growth through epinephrine- and IL-6-dependent NK cell mobilization and redistribution. Cell Metab, 2016, 23(3):554–562. https://doi.org/10.1016/j.cmet.2016.01.011 PMID: 26895752

[17] Dethlefsen C, Lillelund C, Midtgaard J, Andersen C, Pedersen BK, Christensen JF, Hojman P. Exercise regulates breast cancer cell viability: systemic training adaptations *versus* acute exercise responses. Breast Cancer Res Treat, 2016, 159(3):469–479. https://doi.org/10.1007/s10549-016-3970-1 PMID: 27601139

[18] Shimasaki N, Coustan-Smith E, Kamiya T, Campana D. Expanded and armed natural killer cells for cancer treatment. Cytotherapy, 2016, 18(11):1422–1434. https://doi.org/10.1016/j.jcyt.2016.06.013 PMID: 27497701

[19] Hojman P, Gehl J, Christensen JF, Pedersen BK. Molecular mechanisms linking exercise to cancer prevention and treatment. Cell Metab, 2018, 27(1):10–21. https://doi.org/10.1016/j.cmet.2017.09.015 PMID: 29056514

[20] Koelwyn GJ, Wennerberg E, Demaria S, Jones LW. Exercise in regulation of inflammation–immune axis function in cancer initiation and progression. Oncology (Williston Park), 2015, 29(12):908–920, 922. PMID: 26676894 PMCID: PMC4909049

[21] Orange ST, Jordan AR, Odell A, Kavanagh O, Hicks KM, Eaglen T, Todryk S, Saxton JM. Acute aerobic exercise-conditioned serum reduces colon cancer cell proliferation *in vitro* through interleukin-6-induced regulation of DNA damage. Int J Cancer, 2022, 151(2):265–274. https://doi.org/10.1002/ijc.33982 PMID: 35213038 PMCID: PMC9314683

[22] Devin JL, Hill MM, Mourtzakis M, Quadrilatero J, Jenkins DG, Skinner TL. Acute high intensity interval exercise reduces colon cancer cell growth. J Physiol, 2019, 597(8):2177–2184. https://doi.org/10.1113/JP277648 PMID: 30812059 PMCID: PMC6462486

[23] Bigley AB, Rezvani K, Chew C, Sekine T, Pistillo M, Crucian B, Bollard CM, Simpson RJ. Acute exercise preferentially redeploys NK-cells with a highly-differentiated phenotype and augments cytotoxicity against lymphoma and multiple myeloma target cells. Brain Behav Immun, 2014, 39:160–171. https://doi.org/10.1016/j.bbi.2013.10.030 PMID: 24200514

[24] Jones SB, Thomas GA, Hesselsweet SD, Alvarez-Reeves M, Yu H, Irwin ML. Effect of exercise on markers of inflammation in breast cancer survivors: the Yale exercise and survivorship study. Cancer Prev Res (Phila), 2013, 6(2):109–118. https://doi.org/10.1158/1940-6207.CAPR-12-0278 PMID: 23213072 PMCID: PMC3839104

[25] Rogers LQ, Fogleman A, Trammell R, Hopkins-Price P, Vicari S, Rao K, Edson B, Verhulst S, Courneya KS, Hoelzer K. Effects of a physical activity behavior change intervention on inflammation and related health outcomes in breast cancer survivors: pilot randomized trial. Integr Cancer Ther, 2013, 12(4):323–335. https://doi.org/10.1177/1534735412449687 PMID: 22831916 PMCID: PMC3909487

[26] Glass OK, Inman BA, Broadwater G, Courneya KS, Mackey JR, Goruk S, Nelson ER, Jasper J, Field CJ, Bain JR, Muehlbauer M, Stevens RD, Hirschey MD, Jones LW. Effect of aerobic training on the host systemic milieu in patients with solid tumours: an exploratory correlative study. Br J Cancer, 2015, 112(5):825–831. https://doi.org/10.1038/bjc.2014.662 PMID: 25584487 PMCID: PMC4453949

[27] Na YM, Kim MY, Kim YK, Ha YR, Yoon DS. Exercise therapy effect on natural killer cell cytotoxic activity in stomach cancer patients after curative surgery. Arch Phys Med Rehabil, 2000, 81(6):777–779. https://doi.org/10.1016/s0003-9993(00)90110-2 PMID: 10857523

[28] Gómez AM, Martínez C, Fiuza-Luces C, Herrero F, Pérez M, Madero L, Ruiz JR, Lucia A, Ramírez M. Exercise training and cytokines in breast cancer survivors. Int J Sports Med, 2011, 32(6):461–467. https://doi.org/10.1055/s-0031-1271697 PMID: 21380980

[29] Bower P, Brueton V, Gamble C, Treweek S, Smith CT, Young B, Williamson P. Interventions to improve recruitment and retention in clinical trials: a survey and workshop to assess current practice and future priorities. Trials, 2014, 15:399. https://doi.org/10.1186/1745-6215-15-399 PMID: 25322807 PMCID: PMC4210542

[30] Ergun M, Eyigor S, Karaca B, Kisim A, Uslu R. Effects of exercise on angiogenesis and apoptosis-related molecules, quality of life, fatigue and depression in breast cancer patients. Eur J Cancer Care (Engl), 2013, 22(5):626–637. https://doi.org/10.1111/ecc.12068 PMID: 23731173

[31] Clifford BK, Kaakoush NO, Tedla N, Goldstein D, Simar D. The effect of exercise intensity on the inflammatory profile of cancer survivors: a randomised crossover study. Eur J Clin Invest, 2023, 53(7):e13984. https://doi.org/10.1111/eci.13984 PMID: 36920320

[32] Campbell KL, Winters-Stone KM, Wiskemann J, May AM, Schwartz AL, Courneya KS, Zucker DS, Matthews CE, Ligibel JA, Gerber LH, Morris GS, Patel AV, Hue TF, Perna FM, Schmitz KH. Exercise Guidelines for Cancer Survivors: Consensus Statement from International Multidisciplinary Roundtable. Med Sci Sports Exerc, 2019, 51(11):2375–2390. https://doi.org/10.1249/MSS.0000000000002116 PMID: 31626055 PMCID: PMC8576825

[33] Jones L, Bellis MA, Wood S, Hughes K, McCoy E, Eckley L, Bates G, Mikton C, Shakespeare T, Officer A. Prevalence and risk of violence against children with disabilities: a systematic review and meta-analysis of observational studies. Lancet, 2012, 380(9845):899–907. https://doi.org/10.1016/S0140-6736(12)60692-8 PMID: 22795511

[34] Loef M, Walach H. The combined effects of healthy lifestyle behaviors on all cause mortality: a systematic review and meta-analysis. Prev Med, 2012, 55(3):163–170. https://doi.org/10.1016/j.ypmed.2012.06.017 PMID: 22735042

[35] Campbell KL, Brown JC, Lee C, Weltzien E, Li J, Sternfeld B, Campbell N, Vaughan M, Fedric R, Meyerhardt JA, Caan BJ, Schmitz KH. Advances in adherence reporting of resistance

training in a clinical trial during adjuvant chemotherapy for colon cancer. Med Sci Sports Exerc, 2024, 56(6):1186–1195. https://doi.org/10.1249/MSS.0000000000003395 PMID: 38233992 PMCID: PMC11096063

[36] Groen WG, Naaktgeboren WR, van Harten WH, van Vulpen JK, Kool N, Sonke GS, van der Wall E, Velthuis MJ, Aaronson NK, May AM, Stuiver MM. Physical fitness and chemotherapy tolerance in patients with early-stage breast cancer. Med Sci Sports Exerc, 2022, 54(4):537–542. https://doi.org/10.1249/MSS.0000000000002828 PMID: 34961754 PMCID: PMC8920022

[37] Kang DW, Lee J, Suh SH, Ligibel J, Courneya KS, Jeon JY. Effects of exercise on insulin, IGF axis, adipocytokines, and inflammatory markers in breast cancer survivors: a systematic review and meta-analysis. Cancer Epidemiol Biomarkers Prev, 2017, 26(3):355–365. https://doi.org/10.1158/1055-9965.EPI-16-0602 PMID: 27742668

***Corresponding author***
Tatiana Andreea Mihai, Department of Physiotherapy and Sports Medicine, Faculty of Physical Education and Sport, University of Craiova, 146 Brestei Street, 200207 Craiova, Dolj County, Romania; Phone +40251–422 743, e-mail: andreea.ana.mihai@gmail.com

*Received: March 3, 2025*

*Accepted: April 1, 2025*