



**Review Article**

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## Exercise Plays a Crucial Role in Cancer Prevention and Treatment: A Mini-Review

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### Abstract

Cancer is the leading cause of morbidity and mortality worldwide, causing nearly 10 million deaths annually. Evidence suggests that exercise is effective in preventing cancer, improving treatment outcomes, and lowering the risk of recurrence. Therefore, the purpose was to explore how exercise plays a crucial role in cancer prevention, treatment, and enhancement of patient's quality of life. This study also highlighted and evaluated the potential anti-cancer mechanisms at the biomolecular level. Additionally, this review summarized the latest evidence-based physical activity guidelines for cancer patients. The findings suggested that the mechanisms through which exercise reduces cancer risk and progression included cellular repair pathways, reduced systemic inflammation, the metabolic profile of hormones, increased insulin sensitivity, immune system enhancement, increased antioxidant capacity, and direct tumor effects. It was also observed that regular physical activity not only reduced cancer risk but also significantly alleviated adverse effects of cancer treatments and enhanced efficacy of radiotherapy. There is strong evidence on the effect of physical activity on cancer-related fatigue, health-related quality of life, anxiety, depression, lymphedema, and physical function, as well as moderate evidence on bone health and sleep. Current evidence suggests 150 minutes per week of moderate-intensity aerobic exercise and resistance training twice a week for cancer patients. In conclusion, this review indicated remarkable anticarcinogenic benefits of exercise, including reduced tumor incidence, inhibited tumor growth, reduced treatment-related adverse effects, improved treatment outcomes, and lower risk of recurrence. The findings support the integration of exercise into standard oncology care protocols and strategies across all stages of disease. This could significantly improve quality of life and survival rates of cancer patients worldwide. Future research should focus on examining specific biomolecular mechanisms, particularly the role of myokines, to develop therapeutic strategies for cancer patients. Interdisciplinary teams could ensure that exercise interventions are safe, effective, and specifically tailored to patient demographics and types of cancer. Psychosocial and motivational factors should also be considered when designing exercise programs for patients. Additionally, the use of artificial intelligence to promote physical activity among cancer patients should be investigated. Randomized controlled trials and longitudinal cohort studies are also needed to understand the long-term impact of exercise on health outcomes, cancer recurrence and survival.

**Keywords:** Cancer, Exercise, Myokine, Physical Activity, Prevention, Treatment.

### INTRODUCTION

#### Exercise is effective in preventing cancer, improving treatment outcomes, and lowering the risk of recurrence

The global incidence of cancer is increasing rapidly, and the predictions based on demographics indicate a 77 % increase in cancer cases by the year 2050, potentially reaching 35 million <sup>[1]</sup>. Cancer is the leading cause of death worldwide, causing nearly 10 million deaths annually <sup>[1,2]</sup>. The most common cancers are breast, lung, colorectal, and prostate cancer. Approximately one-third of cancer deaths are due to obesity, smoking, excessive alcohol consumption, low fruit and vegetable intake, lack of physical activity, and a sedentary lifestyle <sup>[2]</sup>. The burden of cancer continues to grow, while levels of physical inactivity are alarmingly high. Physical inactivity is associated with various non-communicable diseases, including cancer <sup>[1,2]</sup>. This highlights the urgent need for effective cancer prevention and treatment strategies in healthcare.

Promoting levels of physical activity in the general population could reduce new cancer cases in Europe by as much as 9–19 % <sup>[3]</sup>. Exercise plays a significant role both in the primary and secondary prevention of different types of cancers <sup>[4,5,6,7]</sup>. Additionally, exercise reduces the adverse effects of cancer treatments and improves the patient's quality of life, making it an essential part of daily routines and rehabilitation <sup>[4,8]</sup>. Exercise can also improve the prognosis of cancer patients and prevent cancer recurrence <sup>[5]</sup>.

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A higher level of physical activity is associated with a lower incidence of several types of cancer (see the Figure 1) [7,9]. The strongest evidence of the inverse association between leisure-time physical activity and cancer risk has been observed for breast, endometrial and colon cancers [10]. With various types of cancer, such as breast, colon, stomach, liver, and endometrial cancer, as well as esophageal adenocarcinoma [11,12] is a linear dose-response relationship, according to which a higher level of physical activity is associated with a lower risk of disease. However, no additional benefit was found in the prevention of lung cancer [11] and myeloma [12] at a higher than recommended activity level (7.5-15 MET hours/week).

Individuals who engage in moderate to vigorous exercise for 3 to 4 hours weekly consistently demonstrate 10 % to 20 % lower risk of developing cancer compared to those who are less active. Moreover, the earlier the start of physical activity combined with other healthy lifestyle habits, the stronger the link between physical activity and a lower risk of cancer [13]. Consequently, physical activity and lifestyle counseling are vital components of preventive healthcare.

The purpose of this review was to explore why and how exercise plays a crucial role in cancer prevention, treatment, and enhancement of patient's quality of life. This study also highlighted and evaluated the potential anti-cancer mechanisms at the biomolecular level, particularly focusing on the role of myokines, which mediate the beneficial effects of exercise. Additionally, this review summarized the latest evidence-based physical activity guidelines and recommendations for cancer patients. Notably, the purpose was to achieve new insights and a deeper understanding of exercise oncology and encourage further research and clinical implications of exercise in cancer treatment.

#### **Exercise plays an important role in cancer prevention and progression**

Regular physical activity affects human biochemistry and physiology in various ways, potentially reducing the risk of cancer. Exercise induces beneficial changes in insulin function, lowers inflammation in the body and serum estrogen levels, and improves oxidative, immune, and cellular repair pathways [4,13,14]. It is widely studied that exercise can prevent cancer through various mechanisms, with several key factors illustrated in Table 1.

The specific biomolecular effects of exercise on tumor tissue are still relatively poorly known, and it is still not clear whether acute exercise is more effective than chronic exercise regarding its impact on tumor cells [8,14,15]. However, preclinical mouse experiments have demonstrated that the positive effects of exercise on tumor growth are evident in different types of exercise: high-intensity aerobic [16] endurance [17] and muscle strength training [18]. It is important to note that the response to exercise varies significantly for different types of cancer [19].

Exercise can inhibit the progression of cancer by affecting the malignant tumor and its microenvironment. The current evidence suggests that most of the effects of exercise on malignant tumors are mediated through immunological mechanisms [8]. Exercise (1) *inhibits the progression of cancer* by directly affecting the tumor's microenvironment and internal factors (growth rate, metastases, tumor metabolism, blood circulation, and immunogenicity), (2) *regulates tumor growth* by interacting with systemic agents, (3) *alleviates adverse effects associated with cancer and its treatment*, (4) *improves the efficacy of cancer treatments, prognosis and the patient's quality of life*, and (5) *lowers the risk of cancer recurrence* [4,14,15,21,22].

Studies have found that exercise affects the tumor's microenvironment, making it easier for immune cells to enter the tumor. The result is normalization of blood vessels [19] mobilization and

transfer of NK cells to tissues [22] and reduction of cells that weaken the immune response [7,14,23].

Previously stated effects are partially mediated by bioactive molecules secreted into the bloodstream during exercise, extracellular vesicles (EVs), such as myokines secreted by muscles [15,24]. Of the myokines, irisin seems to be strongly associated with exercise, and thus with weight management and the prevention of several diseases [25]. The concentrations of circulating extracellular vesicles increase rapidly during exercise [26,27,28]. These findings have inspired to investigate their role in the development and progression of cancer [15,29]. Currently, one preclinical study found a direct tumor-suppressive effect of exercise-derived EVs among patients with prostate cancer [30].

Exercise affects the reprogramming of energy metabolism in cancer cells, and EVs are likely to play a significant role in this process. Biomolecules in the serum of an active person can reduce the growth of breast, prostate, and colorectal cancer cells [31,32,33]. This effect is partially mediated by myokines, which affect the body's metabolism, angiogenesis, and inflammatory responses [15]. Myokines act as messengers between muscles and other organs during exercise [34]. Some myokines (oncostatin and irisin) inhibit cell division and/or initiate programmed cell death (apoptosis) in cancer cells, while interleukins (IL-6, IL-10, and IL-15) are involved in the remodeling of the tumor immune microenvironment [35,36].

#### **Exercise enhances the effects of cancer treatments**

Previously, during cancer treatments, patients were advised to rest and avoid vigorous exercise. In recent years, studies have shown that exercise should be an essential part of everyday life and rehabilitation of cancer patients. There are national and international physical activity guidelines for cancer patients [8,37]. According to the current evidence, *American College of Sports Medicine (ACSM)* recommends 150 minutes per week of moderate-intensity aerobic exercise and resistance training twice a week [37]. Moderate to high-intensity endurance training seems to be more effective than light training when the objective is to influence the internal factors of the tumor. Conversely, strength training is crucial for preventing muscle atrophy in cancer patients [20].

The number of tumor cells circulating in the bloodstream seems to predict the risk of cancer recurrence. Exercise may reduce their number and inhibit the formation of metastases [8,38]. Additionally, the pharmacological treatments require blood circulation in the tumor [8]. Regular exercise increases the formation of new blood vessels, i.e. angio- and arteriogenesis, in both skeletal muscles and myocardium [39]. These adaptations have led to improved efficacy of pharmacological treatments in experimental mouse models [40]. The normalization of the tumor's vascular network has been suggested as a potential cancer treatment strategy [41] in which exercise plays a key role.

The efficacy of radiotherapy is based on sufficient oxygen levels in the tumor area, and oxygen deficiency (hypoxia) decreases the tumor's radiation sensitivity and treatment outcomes [8]. Exercise increases blood circulation and oxygen transport to tissues, that can reduce tumor hypoxia and improve the efficacy of radiotherapy [42].

Patients who exercise and are physically fit also tolerate cancer treatments better than those who are in poor physical condition [4,8]. Additionally, intensified training before cancer surgery may enhance the patient's physical condition, leading to greater tolerance of the surgical procedure and shorter hospitalization [43].

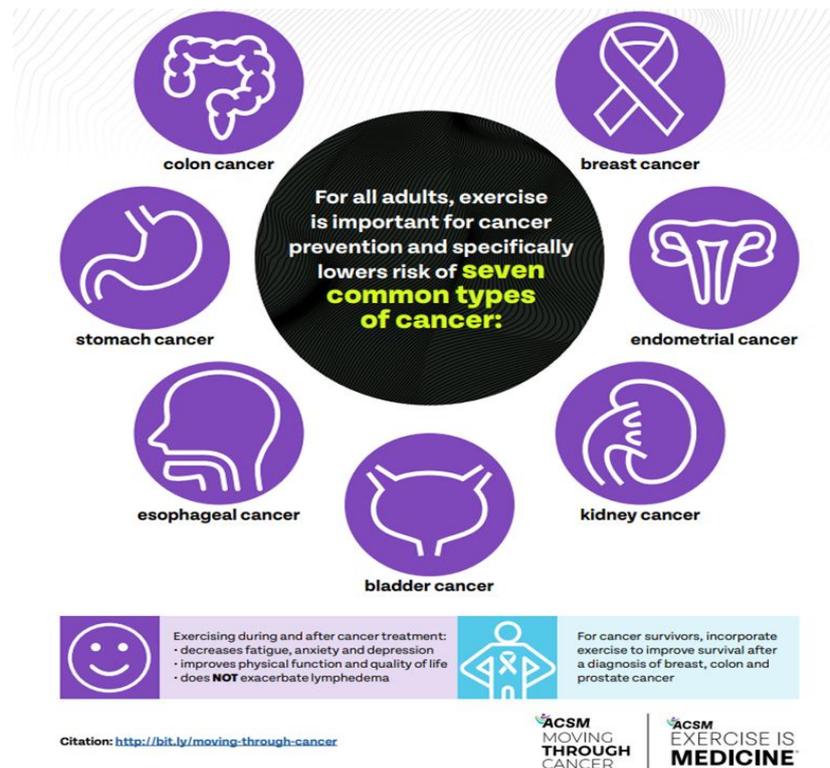


Figure 1: Exercise For Cancer Prevention and Treatment (American College of Sports Medicine, ACSM)

Table 1: Exercise and cancer prevention

Exercise prevents cancer in many ways. Here are some of the key factors:
<b>1. Weight management:</b> Regular exercise helps maintain a healthy body weight. About 4–8 % of all cancers are attributed to obesity. Overweight and obesity are risk factors particularly for ovarian, breast and colon cancer.
<b>2. Hormonal regulation:</b> Exercise affects hormone levels such as testosterone, estrogen, irisin, leptin, and insulin, which can contribute to cancer risk. For example, high estrogen levels have been linked to breast cancer.
<b>3. Regulation of cell growth, repair of DNA damage &amp; apoptosis:</b> Exercise enhances the function and regulation of these factors, which reduces the risk of cancer. Exercise also stimulates cell repair processes and improves tissue regeneration.
<b>4. Epigenetic factors:</b> The activity of proto-oncogenes, such as the RAS gene family, is reduced, which prevents accelerated cell division of cancer cells.
<b>5. Strengthening the immune system:</b> Regular exercise improves the functioning of the immune system, which helps the body identify and destroy cancer cells more effectively.
<b>6. Reduction of inflammatory responses:</b> Chronic inflammation associated with many diseases is reduced. Inflammation can promote the growth and spread of cancer cells. Exercise reduces inflammatory biomarkers in the body, such as cytokines, which can reduce the risk of cancer.
<b>7. Antioxidant effects:</b> Exercise increases the body's production of antioxidants like glutathione, which protects cells from oxidative stress and DNA damage.
<b>8. Improved metabolism:</b> Improved metabolism helps the body process nutrients more efficiently, which can affect the regulation of cell growth. In addition, exercise promotes the elimination of toxins from the body, which can lower the risk of cancer.
<b>9. Mental well-being:</b> The release of endorphins boosts mood by acting as natural painkillers. Endorphins also reduce stress and anxiety, enhance overall sense of happiness. This can improve the quality of life and resilience.
<b>10. Lifestyle improvements:</b> Exercise is often part of a healthy lifestyle, which also includes a healthy diet and not smoking, both of which reduce the risk of cancer.
<b>11. Sunlight &amp; outdoor exercise:</b> Skin begins to produce vitamin D when exposed to UVB radiation from sunlight. Sunlight reduces the production of melatonin, which can improve sleep quality and promote health through enhanced regulation of circadian rhythm, natural sleep-wake cycle. Vitamin D and good sleep also strengthen the immune system.

## Exercise reduces the adverse effects of cancer and treatments

Exercise improves the cancer patient's aerobic endurance and muscle strength, and reduces the adverse effects of treatment, fatigue, cachexia symptoms, anxiety, depression and cognitive disorders during and after treatment. This promotes recovery, functional capacity and quality of life, and reduces the risk of cancer recurrence [4,13,20,44-48]. There is strong evidence on the effect of physical activity on cancer-related fatigue, health-related quality of life, anxiety, depression, lymphedema, and physical function, as well as moderate evidence on bone health and sleep [49].

Cytokines from cancer cells cause muscle atrophy [50] which is further exacerbated by chemotherapy [51], poor nutritional status and physical inactivity [8]. Intervention studies indicate that exercise can positively affect muscle mass and muscle function if muscles are adequately trained during cancer therapies [13,20,52]. Exercise has also been shown to be a beneficial factor in repairing cancer-induced myocardial damage [53].

Breast and prostate cancer patients may face challenges related to weight gain, which can induce mild inflammation within the body [8]. Inflammation and imbalances in sex hormone and insulin levels are associated with a worse prognosis for cancer patients [54]. Exercise inhibits inflammation through the release of anti-inflammatory cytokines during exercise, thereby also reducing the risk of other comorbidities, including cardiovascular diseases [8,13].

Depression, anxiety and cognitive disorders are common adverse effects of cancer treatments that can be prevented [55] or reduced by exercise [4,8,13,20]. Psychological issues may diminish a patient's motivation to adhere to long-term treatments [56], highlighting the essential role of exercise in cancer treatment and recovery.

Fatigue is a common adverse effect caused by cancer therapies that significantly reduces the quality of life, and it can persist long after the end of treatment. Exercise is an effective strategy to prevent fatigue and to alleviate and shorten its duration even after cancer treatments [4,13,20,57].

Cancer causes human suffering at the individual level and high costs to society. From a societal perspective, physical activity can have positive economic impacts [8], as physically fit and active patients require less hospital care [58] and the length of sick leave is shorter during and after cancer treatment compared to less physically active patients [44].

## Limitations of studies

Several research studies, including systematic reviews and meta-analyses, have clearly shown the importance of physical activity and exercise in cancer prevention and treatment, but the quality of studies varies quite a lot. There are some limitations, including selection of patients, heterogeneity concerning patients, cancer type, stage, setting, and exercise type, lack of details for the frequency, intensity, duration, and progression of exercise, a lack of evidence of the impact on cancer outcomes, and challenges in implementation within clinical practice. Additionally, there are scarcely longitudinal cohort studies available to explore the causal relationship between physical activity and cancer recurrence and survival over the long-term, particularly among patients in poor physical condition.

## Clinical implications

Nearly fifty percent of cancers could be prevented if research findings were more effectively integrated into clinical practice [59]. Early detection of cancer, appropriate and timely diagnosis, along with treatment, are essential in decreasing cancer morbidity and mortality. Therefore, it is concerning that adolescents still seem to have low awareness of both lifestyle habits that reduce the risk of cancer and

the symptoms of cancer [60]. Consequently, it is crucial to promote global awareness regarding the beneficial effects of physical activity and other healthy lifestyle habits on cancer prevention and the overall well-being of cancer patients. Exercise should be part of cancer treatment not only in healthcare clinics but also in the daily lives of patients, as it has been demonstrated to be safe throughout all phases of cancer treatment and monitoring, serving as a vital component of recovery and daily living for patients [20].

In the future, there will be a greater emphasis on physical activity as a means of preventing cancer, enhancing treatment results, and aiding in the rehabilitation of cancer patients. As the number of cancer survivors and individuals living with cancer continues to rise, it is necessary that our society develops more holistic protocols and strategies that promote health, functional capacity, and inclusion even after cancer treatment. In this way, we can more effectively support and enhance the overall well-being and quality of life of cancer patients and their family.

Notably, this review gained a deeper understanding of exercise oncology and encouraged further research and decision-making to develop more effective and tailored clinical applications of exercise in oncological treatments in healthcare. The findings advocated the integration of exercise into standard oncological care protocols and strategies across all stages of the disease. It is essential that the exercise program based on general physical activity guidelines is specifically tailored and that monitoring is conducted on an individual basis for each cancer patient. The care of cancer patients must prioritize a holistic approach, offering treatment and support to both the patient and their family. Interdisciplinary teams could ensure that exercise interventions are safe, effective, and specifically tailored to individual cancer patient demographics and different types of cancer.

## Future directions

In the future, exercise oncology requires interdisciplinary collaboration and knowledge of exercise physiology, cancer biology and clinical oncology to provide more personalized targeting strategies and protocols for holistic cancer treatment. Future research should focus on exploring specific biomolecular and cellular mechanisms for developing therapeutic strategies and protocols in different types of cancer. There is need for exploring the role of extracellular vesicles, particularly myokines, in mediating the effects of exercise in the development and progression of cancer. A deeper understanding of these mechanisms is crucial to optimizing exercise programs (i.e. dosage, intensity and training method) that can be individualized based on cancer type, stage, and patient-specific characteristics such as genetic, metabolic, and immunological profiles.

The use of artificial intelligence (AI) will increase in healthcare and exercise oncology in the future, so it is essential to investigate this topic to design more tailored exercise programs and promote physical activity among cancer patients. Additionally, longitudinal cohort studies are needed to understand better the long-term impact of exercise on cancer recurrence and survival. It is important to note that epidemiological studies examining the relationship between physical activity levels and cancer prognosis, as well as the negative impacts of cancer treatments, presents significant challenges regarding participant selection: physically fit patients are likely to exercise more than those who are in poor physical condition. Consequently, there is a necessity for randomized prospective studies to further explore this issue.

## CONCLUSION

In conclusion, this review indicated the remarkable anticarcinogenic benefits of exercise, including reduced tumor incidence, inhibited tumor growth, reduced treatment-related adverse effects, improved

treatment outcomes, and lower the risk of recurrence. Moreover, this review highlighted the potential anti-cancer mechanisms at a biomolecular level, particularly the role of myokines in the development and progression of cancer, but more research is needed.

The findings of this review support the integration of exercise in standard oncology care protocols and strategies across all stages of disease. Translating research findings to best practice guidelines and protocols enhances both inter-professional and intra-professional consensus and minimizing variations in clinical practice. Most importantly, findings may motivate health professionals and policymakers to develop more specifically tailored physical activity guidelines and exercise programs to prevent and treat different types of cancer.

Current evidence suggests that general physical activity guidelines are suitable for most cancer patients, but there is need for more tailored and personalized physical activity guidelines and exercise programs to maximize the therapeutic potential of exercise in oncology. Multidisciplinary collaboration is needed to develop more effective cancer treatments. Notably, a deeper understanding of exercise oncology could significantly improve the quality of life and survival rates of cancer patients worldwide in the future.

Overall, exercise should be part of cancer treatment not only in healthcare clinics but also in daily living of patients. A cancer diagnosis is always a shock, and the experience is unique for each patient, evoking fear and anxiety. Coping with cancer can also be challenging, and therefore psychosocial and motivational factors should be considered when designing exercise programs for cancer patients. The key is to facilitate positive experiences in exercise that promote engagement and generate a sense of personal fulfillment. It is also important to consider the personal values of patients when promoting exercise and other healthy lifestyle habits during and after cancer treatments.

#### Conflicts of interest

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