**World Journal of Pharmaceutical Sciences**
ISSN (Print): 2321-3310; ISSN (Online): 2321-3086
Available online at: http://www.wjpsonline.org/
**Original Article**

# Exercise in cancer and its benefits in cancer survivors

[1]Sharon Thomas*, [2]Mebin Alias, [3]Venkateswaramurthy N

[1]Pharm D Student, [2]Professor, Department of Pharmacy Practice, [3]Professor and Head, Department of Pharmacy Practice, J.K.K. Nattraja College of Pharmacy, Kumarapalayam, India

***Received: 14-11-2020 / Revised Accepted: 19-12-2020 / Published: 22-12-2020***

## ABSTRACT

This review focuses on the relationship between the cancer and physical activity along the continuum of cancer. Detecting a life-threatening disease like cancer and undergoing therapy can cause undesirable distress and interfere with standard of living. There is a wide array of epidemiological evidence to conclude that individuals involved in higher rates of physical activity are less likely to experience a number of cancers compared to those involved in lower levels of physical activity. Exercise enables survivors of cancer deal with and recovers from treatment; exercise can improve long-term cancer survivors' health and increase survival. Physical activity can be effective across the cancer spectrum. During cancer treatment the effects of physical activity are close to those felt after treatment. The results of this review support the belief that exercise is a relevant adjunct therapy in cancer treatment.

**Keywords:** Cancer, Exercise, Physical activity

## INTRODUCTION

Worldwide, more than 10 million people are diagnosed with cancer; with advancement in early detection and management, it can be estimated that a growing number of patients will be alive five years after diagnosis. These people will join the rising number of cancer survivors, estimated at roughly 25 million. [1] This realization has sparked a major research initiative into strategies for enhancing quality of life (QOL), reducing the likelihood of recurrence and other diseases, and expanding longevity in this population. [2] Current cancer treatment, while increasingly effective in enhancing survival, is detrimental in many ways and has harmful short- and long-term physiological and/or psychological effects, including pain, reduced cardiovascular capacity, cancer-related fatigue, reduced quality of life (QOL) and impaired immune function. [3] There are two main types of health issues within the growing population of cancer survivors. The first concerns cancer recurrence and mortality. The second group encompasses the chronic adverse effects of treating cancer. Overweight, obesity and physical inactivity lead to the risk of developing a variety of cancers.

**Address for Correspondence:** Sharon Thomas, Pharm D Student, Department of Pharmacy Practice, J.K.K. Nattraja College of Pharmacy, Kumarapalayam, India

**How to Cite this Article:** Sharon Thomas, Mebin Alias, Venkateswaramurthy N. Exercise in cancer and its benefits in cancer survivors. World J Pharm Sci 2020; 9(1): 14-21.

Recognizing behavioural and environmental risk factors associated with cancer development, informing the public about these risk factors and offering strategies to modify exposure to these risk factors may provide a feasible option to the reduction of cancer burden. [4]

Physical activity has reported effects on human health and well-being, and is associated with decreased mortality risk. Exercise has also proven to have a protective effect on cancer risk. [5] Exercise significantly improves the health and functional outcomes of the cancer population. It also tends to reduce cancer-related adverse effects, has beneficial effects on the whole body and cardiovascular health, and appears to delay the growth of cancer by likely violent action on tumor-intrinsic factors and probably enhancing the effectiveness of the anti-cancer treatment. [6] Exercise interventions are well founded for people undergoing cancer treatment and are safe and beneficial. [7] Evidence of the benefits of exercise has been identified for cancer survivors in psychological and quality of life (QOL) outcomes, fatigue-related diseases, physical functioning, body weight and composition, muscle strength and endurance, immune function and cardiovascular fitness. It can reduce the risk of recurrence of cancer, secondary primary cancers and other chronic diseases and prolong the survival. [8] Cancer survivors who exercise have reduced fatigue, improved quality of life, physical function and body composition. A survivor is defined from the day of the diagnosis of cancer to the end of life. This description is wide and encompasses people with no tumor burden to those with multi-system failure at the end of life. Clearly, exercise needs to be adapted and individualized for each person along the survivorship trajectory. The purpose of this paper is to review the literature and summarize the evidence of physical exercise in preventing cancer, and its effects in survivors at different stages of survivorship. [9]

**Exercise in cancer**

Exercise has been shown to reduce cancer incidence and mortality in more than 25 different cancer types. Exercise in humans is associated with a wide variety of physiological changes, whose extent is determined by the exercise intensity and duration. There is also an increase in cardiac output to satisfy oxygen demands, and a drastic change in blood flow pattern. The metabolic rate is rising, and both glucose intake and production are increasing, as is lactate rates in muscle cells due to anaerobic metabolism. The endocrine system also plays a vital role in coordinating the physiological responses at both rest and exercise. [10] Treatment with cancer causes deep weakening, resulting in lower physical function and impaired quality of life. Physical exercise has enticed increased interest in oncological patient rehabilitation in general, and palliative care as well. Any movement using skeletal muscles is physical activity. Physical activity can be classified into four important subgroups. These subgroups comprise occupational (activity performed at work), household (activity performed at home), transport (activity performed to commute), and recreational or leisure time (activity performed for enjoyment and/or pleasure); physical activity can also differ in intensity, including mild, moderate and intense intensity. [11] Exercise is a planned, structured, and repetitive physical activity that has a purpose and calculated and planned energy expenditure. Exercise can be prescribed during the pre-habilitation phase (time period between cancer diagnosis and initiation of its treatment), habilitation (during treatment), and rehabilitation phase (after therapy in survivors). [12] Studies indicate that physical activity and exercise can help cancer survivors survive longer by: reducing the risk of cancer recurrence or slowing the progression of cancer, and reducing the risk of certain life-threatening diseases, including second primary cancers. Several pathophysiological mechanisms can explain physical exercise's beneficial effects on the prevention of side effects in patients with cancer. According to these mechanisms, PE protects against ischaemia, toxic drug reactions and limits the growth of the tumour. [13] Cancer patients are still more physically inactive than cancer-free adults and 53–70% of cancer survivors are not meeting the prescribed recommendations for physical activity. Exercising, however, is important for oncologically therapied patients with cancer. Exercise can also lead to a substantial delay in tumor growth in conjunction with chemotherapy. There are different types of exercises (aerobic, resistance, strength, weight and effect, balance, flexibility and relaxation) that can be prescribed in different combinations depending on the symptoms. [14] Ideally, exercise should begin at the time of diagnosis, to reduce the cancer symptoms and the progressive side effects of the treatments. If physical activity is provided at the onset of the illness, patients are likely to have the physical capacity to follow and complete activities and be pleased with physical activity, become accustomed to it and sustain regular physical activity throughout and after cancer treatment. [15] Overweight and obesity have been associated with many types of cancer, the ideal method to limit weight gain or loss weight is to unbalance the energy equation by combination of both diet and increasing physical activity.

***Breast Cancer***

Postulated mechanisms underlying the possible effects of exercise and/or activity on cancer progression include the regulation of hormone

levels of metabolic (e.g., glucose–insulin homeostasis markers) and sex-steroid (e.g., estrogen), enhanced immune surveillance, and decreased systemic inflammation and oxidative harm. [16] Breast cancer survivors live for many years and may develop chronic conditions. Interventions incorporating aerobic and resistance exercise as well as alternative forms of exercise (e.g., yoga) are healthy, better-tolerated lifestyle interventions that can not only reduce many of the adverse effects that accompany treatment, but can also show important, clinically relevant improvements in select fitness, physiological and patient-reported outcomes (PROs) in breast cancer patients who are undergoing cancer treatment. [17] The strongest evidence for a correlation between physical activity and cancer outcomes comes from studies of survivors of breast cancer. Nearly all of the studies on breast cancer report that physical activity is associated with breast cancer reduction-specific mortality as well as all-cause mortality; in nearly half of the studies, this risk reduction has been statistically significant and there is evidence of a dose-response effect of decreasing mortality risk with increased activity. [18] When considering the intensity of physical activity needed to minimize the risk of breast cancer, moderate and intense physical activity offers substantial risk reductions in the order of 15%, respectively, and 18%. There is a broad scope and breadth of epidemiological evidence to support the connection between physical activity and risk from breast cancer. The overall decrease in risk by comparing the highest to the lowest physical activity rates is 25%.[19]

***Colorectal Cancer***

Colorectal cancer (CRC) is the third most common type of cancer and the fourth most common cause of cancer-related death worldwide. Obesity and decreased physical activity are associated with colon cancers that have P53 overexpression and KRAS mutation. Physical activity may prevent approximately 15% of the colon cancer. According to some studies, the anti-cancer effect of exercise depends on the carcinogenic exposure and the duration of physical activity. Although the association between exercise and prevention of CRC is definite, the molecular mechanism underlying the protective effect of exercise is yet unknown. The association between exercise and cancer is explained through several mechanisms. These mechanisms include metabolic dysregulation [involving insulin, glucose and insulin-like growth factor (IGF)], sex hormones, adiposity [changes in adipokines (leptin andadiponectin)], oxidative stress and inflammation and impaired immune function. Exercise programs vary according to the type, intensity and frequency of exercise. For colon cancer survivors, supervised exercise is an appropriate program. Initial intensity and duration of the exercise should be determined according to the functional capacity and comorbid status of the patient. Patients should be initially subjected to exercise with less intensity and duration; furthermore, it should be gradually increased based on patients' medical conditions. [20]

***Endometrial Cancer***

There is the epidemiological evidence that physical activity can minimize the risk of endometrial cancer, the fourth leading incident cancer among women in the US. The risk of endometrial cancer is strongly linked with an estrogen: progesterone ratio that is biased towards elevated levels of estrogen; this may result from either an extreme deficiency of progesterone or surplus of estrogen. Physical activity can reduce the risk of endometrial cancer by either limiting exposure to estrogen directly or by reducing the excess adipose tissue. Obesity is a significant risk factor for endometrial cancer and associated with physical inactivity; greater physical activity overall has been associated with a 39 % reduction in risk; which is consistent with an average risk reduction of about 30% found in other studies that assessed total physical activity. Current US recommendations for adults suggest a low-intensity physical activity of 2.5 hours per week, with potential health benefits provided by a moderate exercise of 5 hours per week. Increases in physical activity are likely to reduce obesity, which has been estimated to account for half of all cases of endometrial cancer, thus reducing endometrial cancer incidence. [21]

***Bladder Cancer***

Bladder cancer survivors undergo various treatments that improve survival including, the most common, surgery and also experience a number of side effects that may affect quality of life. [22] Commonly, survivors face sexual and/or urinary dysfunction. Following successful immediate treatment of the tumor, the physical activity level of many patients remains below the minimum levels recommended for health. Encouragement of an increase in physical activity at this stage can thus help to correct limitations of aerobic power, muscular strength and range of motion, enhancing functional capacity and decreasing comorbidity. Some possible mechanisms modifying the risk of bladder tumors in physically active individuals are much as for other body sites, including better weight maintenance, a favorable modulation of immune function, a reduction of chronic inflammation, enhanced DNA repair and apoptosis, and an obesity-related down-regulation of the hormones favoring cell proliferation. Exercise may also lead to a specific detoxification of bladder carcinogens. [23] A potential method of decreasing the morbidity and mortality of bladder cancer is through behavior

change interventions focused on modifiable risk factors. Modulation of lifestyle factors—for example, exercise, weight loss, and diet change may exert beneficial, disease-specific health effects. Thus studies suggest that amount of physical activity may be associated with a lower risk of bladder cancer than a sedentary lifestyle. [24]

***Non-alcoholic fatty liver disease***

The increasing prevalence of obesity has made nonalcoholic fatty liver disease (NAFLD) the most common chronic liver disease. Physical inactivity is related to the severity of fatty liver disease irrespective of body weight, supporting the hypothesis that increasing physical activity through exercise can improve fatty liver disease. Physical exercise has a beneficial effect on NAFLD. Various regimens of aerobic and resistance training have been shown to reduce hepatic fat content through improvements in insulin resistance, liver fatty acid metabolism, liver mitochondrial function, and activation of inflammatory cascades It is said that aerobic exercise, even if done at low intensity and low volume, would have a beneficial effect on the reduction of liver fat. Several randomized trials provide evidence that aerobic exercise indeed reduces hepatic fat content at different intensities and frequencies. Insulin resistance is thought to be a driving force in NASH and its related metabolic syndrome. Improving insulin resistance is among the mechanisms by which physical exercise has been proposed to improve NASH. [25]

***Cardio-toxicity***

Cancer and cardiovascular diseases are the leading causes of death in high-income countries. Cardiovascular complications found in cancer patients are the result of toxicity induced by drugs administered for cancer treatment, so-called 'cardio-toxicity'. Exercise causes cardiorespiratory changes (such as lowering blood pressure) and metabolic changes (such as improving insulin sensitivity, reducing blood lipid levels and enhancing glycemic control) that can prevent cardio-metabolic cancer comorbidities. In addition to pharmacological cardiac protection during cancer therapy it becomes essential to thoroughly investigate the origin of cardiac damage and the strategy to prevent it or to reverse the negative remodelling associated with cardiotoxicity. Exercise is able to reduce some negative effects due to chemotherapy such as fatigue, pulmonary and immune system dysfunction, lymphoedema and toxicity for the heart. [26] Cardiotoxicity prevention refers to the role that exercise has in preventing myocardial damage caused by drugs.

***Lymphedema***

The overall risk of lymphedema for all cancers is estimated to be 15.5% . Lymphedema is an abnormal collection of proteinrich interstitial fluid (lymphatic fluid) that results from lymphatic insufficiency and inadequate lymph transport. Lymphedema is usually classified as primary or secondary. The primary lymphedema has a congenital origin (absence or malformation of lymphatic vessels). The secondary lymphedema has an infective or iatrogenic origin, which can be surgical (because of the removal or damage of lymph nodes) or related to radiation therapy because of the lymph nodes fibrosis. Lymphedema may occur after the surgical treatment of breast cancer, melanoma, gynaecologic and prostatic cancer, head and neck malignancies and sarcoma. The management of lymphedema consists in surgical or non-surgical (conservative) therapy. The conservative treatment is referred to complex decongestive therapy, which includes manual lymphatic drainage, compression therapy and exercise. Physical exercise can be both a treatment and a prevention strategy for lymphedema. A BMI higher than 30 kg/m2 is a significant risk factor for lymphedema, so physical activity is important to prevent this condition. [27] The American National Lymphedema Network (NLN) confirms that a safe form of exercise is an essential part of a fitness program for people with lymphedema and defines five types of exercises: lymphedema remedial exercise, flexibility or stretching exercises, cardiopulmonary exercises, resistance or weightlifting exercises and combined resistance and aerobic exercises. Flexibility or stretching exercises improve the lymphatic function by preserving the range of motion and reducing fibrous adhesions due to surgery or radiation. Cardiopulmonary exercises such as walking, cycling and swimming have not been studied formally as a treatment for lymphedema. Thus exercise is a functional preventive and therapeutic strategy to manage lymphedema because it increases lymphatic fluid flow from the swollen areas. [28]

***Cancer Cachexia***

Cancer cachexia is a para neoplastic syndrome characterised by a progressive loss of skeletal muscle mass (with or without loss of fat mass) that cannot be completely reversed by conventional nutritional support and leads to progressive functional impairment. Approximately 50% of all patients with cancer experience cachexia. The prevalence of cachexia is highest in patients with pancreatic (about 85%), gastric and esophageal cancer while urological (8%), gynaecological (15%) breast and lymphoma cancer patients are less affected. [29] The origin of cancer cachexia is multifactorial and includes reduction of food intake and abnormal energetic metabolism, driven by pro inflammatory cytokines released by tumour cells, such as IFN-γ, TNF-α and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB).

[30] Exercise has a potential role in preventing and treating cachexia. Exercise influences inflammation by lowering the release of pro inflammatory cytokines such as TNF-α and promoting the production of mediators with anti-inflammatory effects, especially myokines, such as interleukin-6 (IL-6). IL-6 improves insulin sensitivity and results in an increase in the concentrations of IL1ra (interleukin-1 receptor antagonist) and IL-10, two anti-inflammatory cytokines and stimulates skeletal muscle oxidative metabolism. [31] Exercise also has an antioxidant effects by activating oxidative damage repairing enzymes. Exercise has an important role on carbohydrate metabolism, since carbohydrates are the major sources of energy during moderate and high-intensity exercise, and furthermore is able to increase muscle glucose uptake and insulin sensitivity also in patients with cachexia when suffer of glucose intolerance and insulin resistance. Progressive resistance training (PRT) is associated with increase of muscle mass and bone mineralisation in both healthy people and elderly sarcopenic individuals. [32] Possible mechanism to explain the positive benefits of resistance training may be the increase of insulin like growth factor 1(IGF-1) and the activation of proliferator-activated receptor gamma coactivator 1 alpha (PGC-1α). The expression of PGC-1α is enhanced during resistance exercise and is associated with fiber-type switching, stimulation of fatty acid oxidation, angiogenesis and resistance to muscle atrophy. [33] Furthermore, a specific form of PGC-1α (PGC-1α4) is probably involved in in skeletal muscle hypertrophy.

**Types of exercise**

The main health related types of exercise are aerobic, resistance and flexibility. Exercise prescription should be tailored according to patient's individual characteristics, to the drugs administered, to the personal history, and to his/her response to exercise, taking into account that different types of training that can be prescribed according also to the patient's choice. The main goals for physical activity in cancer patients are: (a) maintain good physical and social function; (b) optimise the ability to provide an individually adapted treatment; (c) reduce symptoms, with respect to nausea and fatigue in particular; (d) attain an optimal weight and avoid unfavourable weight gain or weight loss. To assess physical activity, there are four parameters that may be estimated: frequency, intensity, time, and type. Frequency is the number of days per week dedicated to engaging in physical activity (d·wk−1). Intensity is how strenuous or how physically demanding a single bout of physical activity is. Time is the length of a single bout of physical activity, measured in minutes or hours (min·d−1 or hr·d−1). Type is the modality of physical activity, and frequently includes aerobic, strength and flexibility activities. [34] Compared with high-intensity exercises, moderate-intensity exercise can be sustained over a longer period of time and provide the required protective benefits, including cardiovascular protection. Several American and Canadian societies recommend 150 minutes of moderate intensity exercise over 3-5 days and at least 2 days devoted to resistance exercise every week. Each exercise session should include a warm-up and a cool-down. The resistance exercise session should involve 2 sets of 8-10 major muscle groups repeated 8-10 times. Flexibility exercises should also include all major muscle groups, and balance exercise should be included for all elderly patients and for those who have balance issues. [35]

***Aerobic activity***

In aerobic training, most of the body muscles usually move in a cyclic manner to allow human locomotion with the necessary energy provided by the aerobic mechanism (i.e. walking, running, bicycling, swimming, cross-country skiing). Aerobic activity is defined by three components that determine the characteristics of aerobic training: (a) intensity, which depends on the energy metabolism rate and which is often indicated as light, moderate or vigorous; (b) frequency of aerobic activity sessions usually expressed in the number of weekly sessions and (c) duration of the activity for each session. According to international guidelines, the duration (minutes of moderate or vigorous per week) may be more important than the other components. [36] American College of Sports Medicine recommends apparently healthy individual to engage in aerobic training 3-5 days/week. In a deconditioned population, however, several shorter exercise sessions per day are generally better tolerated. The intensity recommended for aerobic exercise is 40-85% of maximum heart rate calculated by Karvonen method, which calculates % of heart rate reserve. American College of Sports Medicine recommends that apparently healthy cancer survivors should exercise aerobically between 20-60 minutes, lower range for less fit and old and duration increases according to fitness and age. [37]

***Inspiratory muscle training (IMT)***

IMT can decrease dyspnoea, by strengthening the inspiratory muscles and by offering means for controlled breathing and can also facilitate the increase in the level of activity and improve the quality of life, particularly in thoracic cancer patients. IMT is effective for functional capacity and parameters of medical care if performed for 1–4 weeks, performing 1–3 sessions a week, with moderate intensity (50% for endurance capacity).82 Therefore, IMT seems to be useful and effective,

particularly in thoracic cancer patients and could be prescribed in this specific population. [38]

***Resistance training***

Resistance training is defined as a method to maintain or improve muscular strength, endurance or power, which is performed against relatively high resistance and few repetitions. Resistance exercise is a potent physiological intervention to increase muscle mass and attenuate muscle wasting. The frequency of resistance training sessions, usually expressed as the number of sessions per week. The duration of resistance training should be less than 60 minutes for whole bodywork. The application of resistance training in the upper body improves pain and disability especially in patients treated for breast and head cancer. The effects seem to be beneficial especially in patients with breast, prostate, head and neck cancer, improving muscle function and body composition without any special adverse effects. If the goal is to improve muscle strength and trophism, a series of 8–12 repetitions performed at slow-moderate velocity is considered effective. [39]

***Flexibility training***

Flexibility training is defined as a method of maintaining or improving length of the muscle. Radiation and chemotherapy may cause scar formation in joint, which may result in limitation in range of motion and this limitation can be prevented and normal range of motion can be gained by flexibility training. Flexibility training is given for two to four repetitions with each stretch holding for about 15-30 seconds. [40]

Cancer survivors are not easy to convince in participating physical activities programs, in fact they often reports barriers to physical exercise. Barriers can be classified in disease-specific limitations, such as illness, pain, fatigue; socio-economic barriers such as financial difficulties, lack of time, transportation issues, child care problems and individual barriers such as anhedonia, lowliness, social withdrawal, decreased self-confidence, lack of interest/motivation and the perception of being "too busy" or having "no willpower" . To overcome these barriers survivors should be encouraged by counselling and motivational interviewing with physicians, physical therapists and trainers. Survivors should be encouraged to monitor both the physical activity (e.g., heart rate monitor, perceived exertion) and the daily activities outside the exercise setting and to report the perception of symptoms before, during, and after exercise. This progressive education of the patient provided by the physical therapists and trainer may be the key to keep the patient's adherence to exercise program. [41]

Thus, exercise in cancer patients and survivors should be proposed and started as soon as possible to enhance motivation. A multidisciplinary offer of training, frequency and setting of physical activity as well as the caregiver's support are important to increase exercise adherence. Finally, the most effective type of exercise, optimal exercise frequency and intensity based on the type of cancer should be prescribed and supervised as a therapeutic program like it happens for the type, dose and duration of a drug treatment. [42]

## CONCLUSION

Current cancer treatments, although increasingly efficacious for improving survival, are toxic in numerous ways and produce negative short and long-term physiologic and or psychologic effects, including pain, decreased cardiorespiratory capacity, cancer related fatigue, reduced quality of life, and suppressed immune function. Physical activity has been proposed as a non pharmacologic intervention to combat the physiologic and psychologic effects of treatment in cancer patients. Exercise could represent a suitable combination partner to immune therapy in cancer patients, facilitating improved response rates and more frequent complete lasting responses. Moreover, exercise may directly as a key component of a healthy lifestyle delay or prevent tumor development.

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