Exercise: Preventive and Therapeutic Benefits in Cancer

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Abstract: Cancer is soon expected to overtake cardiovascular diseases as the leading cause of death in the world. As newer and often more expensive cancer treatments become available, several complementary modalities are gaining clinical importance. Exercise is one such modality. Increasing scientific data suggests that exercise, besides helping prevent several cancers, can also help improve outcomes across a range of cancer diagnoses. The mechanisms behind this protection and therapeutic effects are numerous and include changes in body composition, insulin sensitivity, oxidative stress, sex hormone levels, systemic inflammation, immune cell function, and DNA integrity. Exercise is easy to do, is inexpensive, and can be modified to the condition of the patient. This review summarizes the various benefits of structured activity in most major cancers affecting humans.

Keywords: Cancer, exercise, physical activity, sedentary lifestyle, breast cancer, lung cancer. colorectal cancer, prostate cancer, metastasis.

INTRODUCTION

There were nearly 10 million cancer-related deaths in the world, in 2020 [1]. Cancer is now the second leading cause of death globally but is soon expected to become the leading cause [2]. In China, the world's most populous country, cancer is now the leading cause of death [3]. Africa reported 1,109,209 new cases of cancer in 2020 [4] while Asia had 9,503,710 new cancer cases in 2020 [5]. Europe reported 4,398,443 new cancer cases [6], while the National Cancer Institute estimates that there were 1,806,590 new cases of cancer in the USA in 2020 [7]. According to the World Health Organization (WHO) [8], the most common cancer cases in 2020 were: breast (2.26 million), lung (2.21 million), colon and rectum (1.93 million), prostate (1.41 million), skin (non-melanoma) (1.20 million), and stomach (1.09 million) cancer. The most common causes of cancer deaths in 2020 were related to lung (1.80 million), colorectal (935 000), liver (830 000), stomach (769 000), and breast (685 000) cancer.

Most cancers arise from complex pathogenesis involving genetic, environmental, and lifestyle factors [10]. Anand *et al*. reported that up to almost 95% of cancer events are attributable to lifestyle factors such as physical inactivity, cigarette smoking, poor diet, alcohol, and obesity [11]. The lifestyle factors involved are generally modifiable. Physical activity (PA), including structured exercise, is one such modifiable lifestyle [12]. Physical activity before cancer treatment prognosticates better outcomes. It helps mitigate common cancer-related health problems, including anxiety, depressive symptoms, fatigue, and diminished physical functioning [15]. During treatment, it helps improve treatment effectiveness and diminishes treatment-related side effects. Exercise also helps prevent cancer recurrence, both local and distant. The overall quality of life (QOL) improves in these patients, and cancer-related mortality is reduced.

DISCUSSION

Physical activity is defined as any bodily movement produced by skeletal muscles that result in energy expenditure [13], while exercise is a subcategory of physical activity, and is planned, repetitive, and purposive [14]. Physical activities are commonly classified according to the metabolic equivalent (MET) expended. One MET equals an energy expenditure of 1 kcal/kg/hour or an oxygen uptake of 3.5 ml/kg/min. Light-intensity activities expend less than 3 METs, moderate-intensity activities expend 3 to 6 METs, and vigorous activities expend 6 or more METs. Exercises may be aerobic or resistance, but also include stretching, balance and gait workouts, and non-traditional activities such as tai chi and yoga. Activities such as walking, cycling, jogging, and swimming are primarily aerobic exercises. They increase mitochondrial density, insulin sensitivity, oxidative enzymes, blood vessel compliance and reactivity, lung function, immune function, and cardiovascular function [15]. Resistance exercises include workouts with free weights, weight machines, bodyweight, or elastic resistance bands. They result in improvements in muscle mass, body composition, strength, physical function, bone mineral density, insulin sensitivity, blood

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pressure, lipid profiles, and cardiovascular health [16]. Stretching increases the range of motion around joints and enhances flexibility. Balance training can reduce falls risk by improving balance and gait. Activities like tai chi and yoga combine flexibility, balance, and resistance exercises. Besides the physical benefits, all exercises also improve mental and emotional health [17].

Physical activity plays a significant preventive and therapeutic role in cancer [18-21]. In Germany, it is estimated that low physical activity accounts for 6% of all cancers [22], while in the US, it is estimated to account for 2.9% of all cancers [23]. Physical activity and structured exercise have significant benefits in cancer prevention [24]. In a large study (1.44 million participants and 186,972 cancers), significant cancer prevention in 13 common cancers was noted with exercise when high vs low levels of leisure-time physical activity was compared [24]. These included cancers of the esophageal (adenocarcinoma) (Hazard Ratio or HR= 0.58), liver (HR= 0.73), lung (HR= 0.74), kidney (HR= 0.77), gastric cardia (HR= 0.78), endometrium (HR= 0.79), colon (HR= 0.84), head and neck (HR= 0.85), rectum (HR= 0.87), bladder (HR= 0.87), and breast (HR= 0.90). There was also a reduction noted in myeloid leukemia (HR= 0.80), myeloma (HR= 0.83) [24]. Leisure-time physical activity, however, increased the risks of malignant melanoma (HR=1.27) and prostate cancer (HR=1.05) in this study [24]. A more recent umbrella review, which included 19 reviews, 26 meta-analyses, and 541 original studies, also concluded that regular physical activity is beneficial in preventing several cancers, including those of the colon, breast, endometrium, lung, esophagus, pancreas, and meninges [25]. Prevention benefits even occur with minimal amounts of exercise, and there appears to be a dose-dependent relationship [26]. Further, long-term or lifetime physical activity also influences cancer prevention, as the process of normal cells becoming invasive tumors usually takes many years [27]. Exercise therapy before the initiation of chemotherapy, or before surgical intervention, is also associated with improvements in tolerance to treatment [28].

Exercise during treatment may increases treatment efficacy, be it chemotherapy, immunotherapy, or radiation therapy, by decreasing tumor hypoxia [29-31]. It also helps reduce treatment-related side effects. These include anxiety, depression, reduced bone density, fatigue, lymphedema, poor functional status, disturbed sleep, and poor QOL. Exercise may also help ameliorate certain other problems related to cancer and its treatment. These include cardiotoxicity, chemotherapy-induced peripheral neuropathy, balance impairment, falls, cognitive dysfunction, nausea, and pain. It also helps improve sexual dysfunction often noted in prostate cancer following androgen deprivation therapy (ADT). Exercise may also help retard tumor progression [32]. Animal studies have reported a reduction in tumor mass with high-intensity training. Exercise in humans has also been shown to reduce cell proliferation and increase markers of apoptosis. Higher levels of exercise have been noted to cause a statistically significant reduction in cancer recurrence (local and distant) in patients with three common cancers – those involving the breast, colorectal tissue, and prostate. Cormie *et al*. in a meta-analysis review calculated that the pooled HRs ranged from 0.79 to 0.76 for this reduction [33]. Distant metastases are responsible for 90% of all cancer-related deaths [34], and exercise helps prevent metastasis [35]. Exercise increases tumor vasculature, and this appears to retard the spread of tumor cells to distant organs [36]. Animal studies indicate that exercise may prevent brain metastasis in lung cancer and lung metastasis in breast cancer. Precancer exercise and exercise during and after cancer treatment also improves longevity [37]. Higher levels of physical activity appear to be more effective in reducing cancer mortality. Cornie *et al*. in a meta-analytic review calculated that highly active and exercising cancer patients had a lower relative risk of all-cause mortality (pooled HRs range from 0.75 to 0.52) [33]. Another study found a mortality reduction of 48% in nearly 14,000 cancer survivors, at least three years post-treatment with adherence to both aerobic and resistance physical activity guidelines [38]. Although both aerobic and resistance exercise help individually, data supports the combination of aerobic and resistance exercise has a synergizing anti-cancer effect [39].

Cancer and its treatment, usually cause physical discomfort and mental deterioration, reducing the desire and ability to exercise [40]. However, most studies find exercise safe during and after treatment and have reported negligible adverse effects [41]. Most international institutions recommend that adults engage in moderate-intensity physical activity for at least 30 minutes a day for five days a week, or exercise at a high intensity for at least 20–30 minutes, three or more days a week [42]. Regular exercise is also recommended by various oncology health experts and organizations. A recent set of guidelines from the American College of Sports Medicine International

Multidisciplinary Roundtable on Physical Activity and Cancer Prevention and Control in 2018 recommend that cancer patients partake in moderate-intensity aerobic training at least three times per week, for at least 30 min each session, for 8 to 12 week [43]. They also recommend adding resistance training to aerobic training, at least two times per week. The resistance exercises should consist of two sets of 8 to 15 repetitions per set, per exercise. Each repetition should be at least 60% of the maximum weight the patient can lift or press for a given exercise. Supervised exercise is associated with better compliance [44]. More than 40% of the patients diagnosed with cancer have comorbid diseases (such as diabetes, obesity, chronic obstructive pulmonary disease, heart failure, and coronary artery disease) [45]. Exercise in cancer patients also helps diminish the harmful impact of these comorbid non-communicable diseases [46].

Physical activity induces a reduction in adipose tissue [47], improves insulin resistance [48], reduces the inflammatory state, and beneficially regulates the immune system [49]. Exercise also helps modulate endogenous sex hormone levels [50], enhances resistance to oxidative stress [51], and helps repair DNA damage [52].

EXERCISE AND LUNG CANCER

Exercise helps reduce the risk of lung cancer by 20-30% in women and 20-50% in men [53]. Preoperative exercises in lung cancer improve pulmonary function before surgery [54]. These help in reducing the duration of hospital stay and help reduce postoperative complications after lung resection surgery [54]. Postoperatively, these patients report a significant improvement in QOL [55]. Studies in animals suggest that brain metastasis in lung cancer may also be reduced with exercise [56].

EXERCISE AND BREAST CANCER

Several studies have demonstrated that physical activity results in lowering the breast cancer risk [57]. Women who are the most physically active have a 25% less chance of getting breast cancer when compared to those that are the least physically active. Even recreational and household activities of moderate-intensity and sustained over a lifetime appeared to be cancer preventive. Exercise during the treatment of breast cancer helps mitigate treatment-related side effects such as fatigue, stress, depression, and lymphedema [58]. Exercise helps improve cardiorespiratory fitness, increase muscular strength, and improve the quality of life in these patients [59]. It helps reduce metastasis and improves overall survival.

EXERCISE AND COLORECTAL CANCER

Exercise also helps prevent colon cancers [60]. A meta-analysis showed that physical activity resulted in a 24% decrease in colon cancer risk [61], while another study found that exercising 7 hours a week reduced the risk by 40% [62]. Physical activity, especially in higher volumes, is associated with less fatigue, better bowel function, more salubrious sleep, lesser stress, and improved QOL [63]. However, up to 90% of colon cancer survivors do not engage in the recommended minimum volume of 150 min/week of physical activity [64], despite several studies correlating higher volume of exercise (up to 300 min/week) with improved disease outcomes in these patients [65]. Increased physical activity has also been associated with significant reductions in mortality for survivors of colorectal cancer [66].

EXERCISE AND PROSTATE CANCER

Several systemic reviews and meta-analyses have suggested that total physical activity, including leisure-time physical activity, leads to a decrease in the risk of developing prostate cancer [67]. In addition, epidemiological studies have shown that exercise, after a prostate cancer diagnosis, results in better outcomes with treatment [68]. Prostate cancer treatment is often associated with fatigue, and diminished quality of life, and exercise helps mitigate these [69]. In patients on ADT, exercise helps control abdominal fat and the BMI [70]. The patients develop better muscle strength and become more exercise tolerant [70]. Sexual function and QOL also improves. In patients with bone metastasis, exercise by improving physical fitness helps decrease the risk of developing pathological fractures, hypercalcemia, bone marrow suppression, and nerve compression or spinal cord compression [71]. Mortality is also reduced by about 38% between the highest versus lowest levels of physical activity in these patients [72].

EXERCISE AND STOMACH CANCER

In a 2016 meta-analysis, the risk of gastric cancer was reduced by approximately 19% for individuals engaging in highest versus lowest levels of activity [73]. More recently, Xie *et al.* found that when patients with high PA were compared to those with low PA, there was a reduction of 17% in gastric cancer in the former [74]. Gastric cancer patients also tend to become

sarcopenic and frail, and a combination of resistance and endurance exercises improves muscle mass and increases strength and function in these patients [75]. Exercise done preoperatively helps improve postoperative outcomes [76]. Exercise also helps combat functional decline that gets aggravated with chemotherapy and chemoradiation in these patients [77].

EXERCISE AND LIVER CANCER

Physical activity is inversely related to the risk of liver cancer [78]. In a large meta-analysis (8440 liver cancer cases) high vs low physical activity reduced the risk of liver cancer by 25% [79]. Sedentary behavior modification by increasing walking times and decreasing screen times also appears to reduce the risk of liver cancer [80]. An umbrella review was inconclusive to support a beneficial effect of physical activity for lowering the risk of liver cancer [81]. However, the beneficial effects of exercise on retarding liver cancer were recently documented in mice [82]. Perioperative exercise therapy for patients with hepatocellular carcinoma improves physical fitness and shortens hospital stay and results in an earlier resumption of daily exercise after hepatectomy [83]. Studies have also noted an inverse association between total physical activity and liver cancer mortality [79].

EXERCISE AND ESOPHAGEAL CANCER

Physical activity decreases esophageal cancer [84]. Poor physical fitness preoperatively results in poor tolerance of peri-operative oncological treatment, with increased toxicity, longer hospital stay, and long-term adverse events [85]. They also demonstrate decreased long-term survival [86]. Better physically fit patients do better [87]. Perioperative exercise to improve physical conditioning reduces adverse outcomes [88]. Post-operative exercises also help improve their QOL [89].

EXERCISE AND THYROID CANCER

Daily walking reduces the risk of thyroid cancer [90]. Thyroid hormone replacement after thyroidectomy may result in fatigue, anxiety, and poor QOL, which is mitigated by a home-based exercise program [91].

EXERCISE AND URINARY BLADDER CANCER

Keimling *et al*. found a reduced risk of bladder cancer among individuals with the highest levels of physical activity (Risk Ratio=0.86) [92]. Another study reported a 47% decreased risk of bladder cancer death in exercising individuals [93].

EXERCISE AND KIDNEY CANCER

A meta-analysis, published in 2013, reported that the risk of renal cancer was lower for individuals engaging in the highest versus lowest categories of physical activity level (RR=0.88) [94]. Exercise also helps control or reduce obesity, which independently increases kidney cancer risk and kidney cancer mortality [95]. In multivariate analyses of 222,163 individuals, "any physical activity" was associated with 50% fewer kidney cancer deaths than that seen in non-exercisers [95]. Exercise improves QOL in kidney cancer patients [96].

EXERCISE AND GYNECOLOGICAL CANCER

There is substantial scientific evidence that physical activity, amounting to >30 min per day, reduces the risk of endometrial cancer [97]. This reduction was estimated to be 25% with moderate and vigorous recreational exercise [98]. Physical activity in cervical cancer can result in improvements in fatigue and sexual functioning. Cervical cancer patients may also notice an improved quality of life and enhanced survivorship by increasing physical exercise [99].

EXERCISE AND SKIN CANCER

Physical activity outdoors increases the risk of skin cancer [100] due to excessive exposure to solar radiation [101]. This can be reduced by exercising indoors [102]. Outdoor exercising patients should protect themselves against UV radiation and comply with regular skin examinations to detect early skin cancer, thereby reducing the incidence, morbidity, and mortality of skin cancer [102].

EXERCISE AND OTHER CANCERS

There is evidence suggesting an association between higher physical activity and decreased risks of hematologic cancers (myeloid neoplasms (myelodysplastic syndromes, acute myeloid leukemia, myeloproliferative neoplasms, chronic lymphocytic leukemia, small lymphocytic lymphoma, and mature B cell lymphomas), head and neck cancers, and pancreatic cancers [103]. The relationship between physical activity and ovarian cancer remains unclear [104].

CONCLUSION

Physical activity appears to play an important role in cancer. It not only plays an important preventive role, but it also retards the progression of several cancers, reduces recurrence, and increases survival. It helps

attenuate cancer treatment-related side effects. Besides, it also helps diminish the adverse impact of chronic co-morbid conditions that many of these patients have. Exercise also helps improve the psychological health of these patients. Overall, cancer patients notice an improved health-related quality of life with exercise. Both aerobic and resistance exercises are beneficial. Stretching, flexibility, balance, and non-traditional exercises like yoga and tai chi provide added benefits. Exercise should be of at least moderate intensity. More exercise is better as there appears to be a dose-dependent relationship. Overall, the benefits of exercise in cancer are extremely persuasive. A structured exercise program, ideally supervised, should be an integral component of the "standard of care" in cancer management.

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