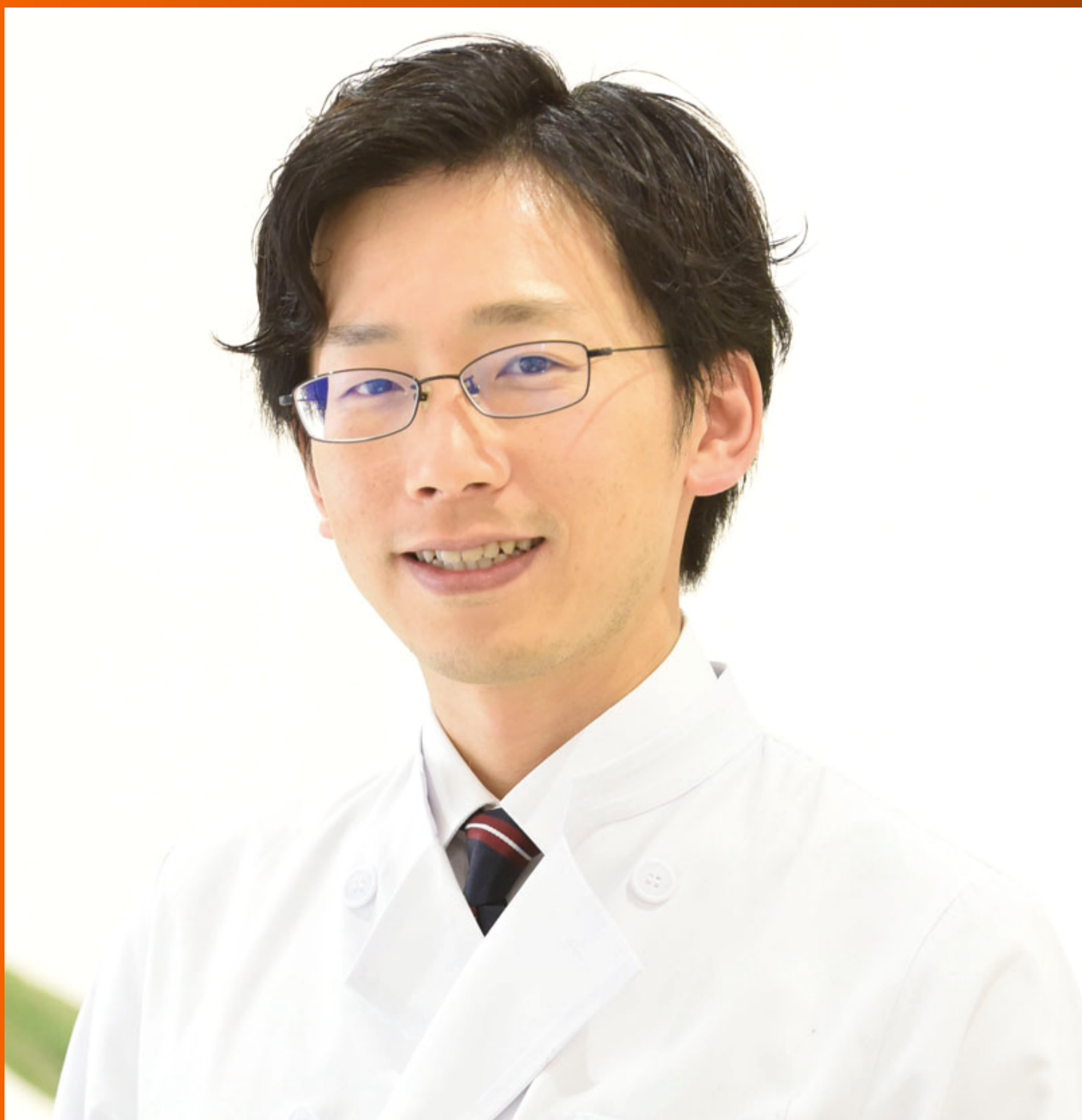


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Effect of exercise on colorectal cancer prevention and treatment

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Abstract

In recent years, because of improved cancer screening, detection and treatment modalities, a rapid increase in the population of colorectal and other cancer survivors has been observed. The increasing population has justified the requirement of preventive strategies such as lifestyle modifications with regard to obesity, physical activity, diet and smoking. Physical activity may prevent approximately 15% of the colon cancers. Furthermore, several observational studies have demonstrated the efficacy and dose-dependent and anti-cancer effects of exercise on decreasing the mortality and risk of recurrence before and after the colorectal cancer (CRC) diagnosis. However, the required exercise dose, type and intensity are yet unclear. The results of randomised prospective studies are expected to determine the optimal amount, type and intensity of exercise and formulate the most appropriate exercise plan and guidelines, according to the requirements and comorbidities of the patients. In addition, recent studies have focused on the molecular and genetic mechanisms underlying the effect of physical activity on disease outcomes and recurrence rates. This review aimed to investigate the effects of physical activity and the biological basis of these effects in preventing the risk and recurrence of CRC and decreasing the hazards of cancer and cancer treatment.

Key words: Colorectal cancer; Exercise; Physical activity

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Core tip: This review aimed to investigate the effects of physical activity and the biological basis of these effects in preventing the risk and recurrence of colorectal cancer (CRC) and decreasing the hazards of cancer and cancer treatment. Several observational studies have demonstrated the efficacy and dose-dependent and anti-cancer effects of exercise on decreasing the mortality and risk of recurrence before and after the CRC

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diagnosis. However, the required exercise dose, type and intensity are yet unclear. The results of randomised prospective studies are expected.

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INTRODUCTION

Colorectal cancer (CRC) is the third most common type of cancer and the fourth most common cause of cancer-related death worldwide^[1,2]. A significant improvement has been observed in the 5-year survival rates with early screening programs, new treatment modalities and individualised treatments. The 5-year survival rates of patients with stage 1-3 CRC, accounting for approximately 75% of patients with CRC, has approached 65%^[3]. Although long-term survival is poor in metastatic disease, patients have been living for more than 2 years because of new developments in treatment strategies^[4].

The aetiology of CRC is multifactorial. In addition to genetic factors, lifestyle and environmental risk factors have substantial effects on CRC development. Several risk factors have been identified for CRC (low-fibre and high-fat diet, sedentary lifestyle, diabetes, obesity, smoking, alcohol, advanced age and inflammatory bowel disease). In recent years, the increase in CRC incidence is attributed to the increase in the elderly population, changes in dietary habits and increased risk factors such as smoking, low physical activity and obesity. Despite the advances in treatment strategies, new therapies have limited impact on cure rates and survival. Therefore, a tendency towards selecting adjuvant treatment strategies such as physical activity and exercise has been observed^[4-6].

Epidemiological studies have shown that lifestyle factors and obesity affect the development of various types of cancer, particularly CRC^[7]. A synergistic association is observed between physical inactivity and obesity. The International Agency for Research on Cancer (IARC) has reported that 25% of all the cancer cases worldwide are caused by obesity and sedentary lifestyle^[8].

Obesity and decreased physical activity are associated with colon cancers that have P53 overexpression and KRAS mutation^[9,10]. Physical activity may prevent approximately 15% of the colon cancers^[8]. An umbrella review, including 19 reviews, 26 meta-analyses and 541 original studies, evaluating physical activity and cancer risk, has shown that regular physical activity is beneficial in preventing 7 types of cancers (colon, breast, endometrium, lung, oesophagus, pancreas and meningioma)^[11]. The effect of physical activity on cancer risk is much stronger in breast and colon cancer than in the other types of cancers^[12]. In recent studies, a dose-dependent effect of exercise has been reported^[13,14].

More than 40% of the patients diagnosed with CRCs have comorbid diseases (diabetes, obesity, chronic obstructive pulmonary disease and heart failure)^[15]. Physical activity decreases the risk of developing comorbid diseases in patients with CRC and improves the disease outcomes in patients with comorbid diseases. Several studies have been conducted regarding the effects of exercise on cancer prevention and the outcome in patients with cancer. Most studies focus on CRC and breast cancer. Furthermore, observational studies regarding cancer prevention and exercise are predominant and have often tested aerobic exercise programs. In these studies, physical activities were generally measured as metabolic equivalents hour/week (MET-hour/week). Because these studies include heterogeneous physical activity applications and are survey-based and subjective, significant errors in physical activity measurement have been reported. The studies showed the benefit of increased physical activity after the known predictors (stage, tumour differentiation and treatment status) were adjusted in the analysis. Furthermore, most studies suggested that the beneficial effect of physical activity is independent of the body mass index (BMI) and physical fitness. In recent years, exercise in patients with CRC is used as both primary and secondary prevention and CRC treatment.

CRC AND PRIMARY PREVENTION

Recently, several studies regarding cancer prevention and treatment strategies are directed towards novel approaches alternative to pharmacological treatments. Physical activity has been known to decrease the incidence of age-related chronic diseases such as cardiovascular disease, diabetes, hypertension and metabolic syndrome. Recent studies have additionally revealed that exercise aids the prevention of CRC.

The protective role of physical activity can be correlated with the incidence of precancerous colorectal polyps^[16]. In an epidemiological study, it was observed that those who exercised for ≥ 1 h per week had a lower prevalence of colon polyps and adenoma than those who exercised for < 1 h^[17]. In this study, exercise decreased the risk of polyp development throughout the entire colon, regardless of a specific area of the colon. In another study, exercise was reported to decrease the total number of intestinal polyps by 50% and the number of large polyps by 67%^[18].

A meta-analysis showed that physical activity resulted in a 24% decrease in colon cancer risk [risk ratio (RR): 0.76, 95% confidence interval (CI): 0.72–0.81]^[19]. In a population of more than 150000 people, 940 colon and 390 rectal cancer cases were detected in a 6-year study period of an epidemiological study, evaluating the association between the risk of colon cancer and physical activity. In this study, 21% of men and 16.5% of women were physically active (> 7 h of regular physical activity), and it was reported that the risk of colon cancer decreased by 40% in the people exercising 7 h a week^[20,21].

In the studies evaluating the association between CRC and physical activity, the intensity, type and area-specific effect of physical activity have been evaluated. A meta-analysis showed that increasing doses of physical activity considerably decreased the risk of colon cancer^[20].

In a study by Mahmood *et al*^[21], no statistically significant decrease in the risk of CRC was detected with occupational, transport and household activities. However, recreational activity significantly decreased the risk of CRC. Although physical activity decreases the risk of colon cancer, the association between physical activity and colon cancer are yet unclear. Furthermore, the duration and intensity of physical activity required to optimally decrease the risk of CRC are unknown.

In recent studies, the epidemiological differences in proximal and distal colon cancers and different genetic and environmental risk factors are reported to show different molecular features. Accordingly, modified treatment approaches have been adopted for proximal and distal colon cancers^[22]. In a study, it was reported that physical activity had more effect on the risk of distal colon cancer than that of proximal colon cancers^[23].

In a meta-analysis study involving 21 studies, the association between physical activity and colon cancer did not differ with the anatomical location^[14]. Moreover, data regarding rectal cancer are insufficient^[24]. Some studies describe a similar decrease in the risk of colon cancer, whereas other studies have not demonstrated the benefit of physical activity in rectal cancer^[19,25,26]. In a meta-analysis, no significant decrease in risk was found with regard to the incidence of rectal cancer among physically active subjects (RR: 1.15, 95%CI: 0.83–1.64)^[27]. In a recent meta-analysis, higher physical activity was found to be associated with a decreased risk of colon by 16% and rectal cancer by 13%^[28].

According to some studies, the anti-cancer effect of exercise depends on the carcinogenic exposure and the duration of physical activity. In a preclinical study, exercising during and before chemical exposure in a chemically induced intestinal tumour rat model resulted in a significant decrease in the number of tumours. However, exercise following chemical exposure did not have any effect^[29].

In early physical activity and cancer studies, physical activity has been reported to decrease the risk of colon cancer, particularly in men; however, it does not decrease the risk in women^[30]. Mechanisms associated with gender differences are yet unknown. Sex hormones are considered to have a protective effect against colon cancer; thus, the difference observed in the studies may be because of a decreased protective effect caused by decreased estrogen levels in women who exercise more. However, in the meta-analysis of 20 studies in 2011, no difference was observed between the genders in terms of physical activity and the risk of CRC^[31]. Moreover, in a study involving postmenopausal women, women undergoing hormone replacement therapy were shown to have a lower risk of colon cancer, and physical activity did not provide any additional benefit. However, it has been shown that physical activity has a protective effect against colon cancer in postmenopausal women who are not undergoing hormone replacement therapy^[32]. In a meta-analysis evaluating 19 cohort studies, the risk of CRC in physically active women and men was reported to be decreased by 29% and 22%, respectively^[33].

CRC AND SECONDARY PREVENTION

Because of early diagnosis and advances in the treatment of cancers, > 25 million people have been diagnosed with cancer worldwide, and this number is increasing each day. This population has been estimated to increase to > 75 million in the next 3 decades^[34]. Despite positive developments, patients experience several long-term health issues and physical and psychological issues following cancer treatment. Compared with the general population, studies have shown that secondary malignancy, cardiovascular disease, diabetes, osteoporosis, sleep disorders, anxiety, depression and decreased functional capacity exhibit a higher risk, in addition to the risk of recurrence, in patients with cancer. These comorbid conditions can be caused by cancer treatment, in addition to genetic predisposing and lifestyle factors^[35,36]. In recent years, there has been an increasing awareness of lifestyle modifications because of the increased population of cancer survivors.

With regard to primary prevention, the role of physical activity during and after CRC treatment is yet unclear. Compared with other cancer survivors, CRC survivors have been observed to have a higher rate of physical inactivity^[37]. In one study, 68% of CRC survivors were physically inactive after a curative treatment^[38]. Despite the benefits of physical activity, only 23.5% of CRC survivors followed the exercise guidelines^[39]. In another study, 21%–42% of CRC survivors could exercise according to the guidelines recommended by the American College of Sports Medicine (ACSM)/American Cancer Society (ACS)/National Comprehensive Cancer Network, 6 months following the curative treatment^[40]. Adherence to exercise and dietary guidelines in patients with cancer is associated with a lower incidence of cancer and lower cancer-specific and all-cause mortality^[41].

Despite advances in the diagnosis and treatment, the rate of recurrence for locally advanced colon cancer is 40%^[42]. In addition to the risk of recurrence, CRC survivors experience the late and long-term effects of cancer treatment^[43,44]. Lifestyle interventions such as an improved diet and exercise are recommended to improve the side effects of cancer and cancer treatment. Physical activity improves clinical conditions, such as weakness, quality of life, muscle strength, lymphedema, depression, functional status, and decreases the risk of recurrence of cancer before and after the diagnosis of CRC and cancer-specific and overall mortality^[38,45–47]. Because exercise decreases the risk of developing chronic diseases such as cardiovascular disease and diabetes, there is a decrease in the all-cause mortality^[48].

In a meta-analysis evaluating 16 breast and 7 CRC studies comparing low and high levels of post-diagnostic physical activity, a 42% (RR: 0.58, 95% CI: 0.48–0.70) decrease in the risk of all-cause mortality and 39% decrease in CRC-specific mortality (RR 0.61, 95% CI: 0.40–0.92) were detected^[49]. In CRC survivors who adhered to the new guidelines, CRC-specific mortality has been shown to be 10%–40% less and all-cause mortality to be 20%–50% less^[50–53]. Clearly, post-diagnostic physical activity is associated with an improvement in disease outcomes in patients with CRC; however, whether the pre-diagnostic physical activity affects the CRC survival remains unclear^[54]. A meta-analysis evaluating prospective cohort studies has shown a 25% decrease (HR: 0.75, 95% CI: 0.65–0.87) in CRC-specific mortality in those who participated in any physical activity at any level before diagnosis compared with those who did not participate at all. Furthermore, the pre-diagnostic physical activity decreased the all-cause mortality^[55]. The clinical benefit rate increased when the level of physical activity was increased. Whether the effect of the post-diagnostic physical activity on CRC survival is influenced by the pre-diagnostic physical activity remains unknown. A new meta-analysis included both pre-diagnostic (CRC-specific mortality; HR: 0.79, 95% CI: 0.71–0.89, total mortality HR: 0.81, 95% CI: 0.72–0.91) and post-diagnostic physical activity (CRC-specific mortality; HR: 0.77, 95% CI: 0.63–0.94, all mortality HR: 0.71, 95% CI: 0.63–0.81) and confirmed its association with improved disease outcomes^[56]. Furthermore, a recent study demonstrated the benefit of both pre- and post-diagnostic activity in postmenopausal women with CRC^[57].

CRC is associated with multiple gene mutations (such as *APC*, *KRAS*, *PIK3CA* and *TP53*). Recent studies to identify patients with CRC who may benefit from exercise evaluated the association between physical activity and cancer outcomes using molecular [*KRAS*, *PIK3CA*, *BRAF* and microsatellite instability (MSI)] or genetic markers [P27 (CDKN1B)-positive, B-catenin (CTNNB1)-negative, PTGS2 (prostaglandin-endoperoxide synthase 2/COX-2)-positive or the insulin receptor substrate (IRS1)-low/negative protein expressions]^[58–62]. The study results showed that P27, B-catenin, COX-2 and IRS1 expression significantly modified the association between the post-diagnostic physical activity and CRC-specific survival. Physical activity significantly has been shown to improve CRC-specific survival after diagnosis in patients with tumours with increased P27 and COX-2 expression and decreased B-catenin and IRS1 expression^[58–62]. Hardikar *et al*^[63] showed that the beneficial effect of

physical activity was not specific to the molecular phenotype of CRC (*BRAF* mutation, *KRAS* mutation and MSI status).

To date, few studies have evaluated the feasibility and reliability of increased physical activity compared with the standard levels. In a study by Brown *et al*^[5], stage 1–3 colon cancer survivors were included in anaerobic exercise program for 150 min/wk (14 patients, low doses) or 300 min/wk (12 patients, high doses) for 6 months, and 13 patients were randomised into the control group. In this study, changes in the prognostic markers such as soluble intercellular adhesion molecule (sICAM-1) and vascular adhesion molecule 1 (sVCAM-1), which are associated with early death and disease recurrence, were evaluated among colon cancer survivors^[64,65]. Increased exercise and physical activity (300 min/wk) were associated with decreased mortality and risk of recurrence in CRC survivors. Furthermore, sICAM-1 reduction was achieved in both exercise arms; however, sVCAM-1 did not decrease. Moreover, sICAM-1 may be associated with the anti-cancer effect of exercise; however, this finding requires further confirmation^[66].

Although observational studies have shown the beneficial association between physical activity and survival after CRC treatment, no randomised controlled trials have been conducted. The first prospective phase 3 randomised clinical trial, Challenge Trial (the Colon Health and Lifelong Exercise Trials), continues to evaluate the effect of 3-year exercise on survival in stage 2 and 3 CRC survivors^[67]. Furthermore, there are many on-going studies focusing on CRC and exercise (Table 1).

EXERCISE IN PATIENTS WITH CRC UNDERGOING TREATMENT

Reportedly, exercise improves the surgical tolerance of CRC and decreases the hospital stay after surgery^[68]. Exercise before CRC surgery may improve postoperative results. However, one review concluded that whether exercise before CRC surgery reflected improvement in peri- and post-operative outcomes was unclear^[69]. A phase 3 randomised prospective study, PHYSSURG-C study, evaluating the effect of pre- and post-operative physical activity on the post-operative morbidity and mortality after CRC surgery is on-going (NCT 02299596)^[70]. Exercise has been shown to improve the quality of life and decrease few side effects in several patient groups receiving adjuvant therapy^[44]. In addition, exercise increases the completion rate of chemotherapy in patients with CRC^[71].

Neoadjuvant chemotherapy and radiotherapy can cause severe acute toxicity in locally advanced rectal cancer. Few studies have shown that exercise is feasible and safe during neoadjuvant therapy in rectal cancer^[72]. The EXERT study, which is evaluating the effect of exercise on the clinical outcomes and side effects of exercise performed during and after neoadjuvant treatment in locally advanced rectal cancer, is on-going (NCT03082495)^[73].

In patients with cancer, the disease itself and each treatment modality applied (surgery, chemotherapy and radiotherapy) can create specific side effects and complications that affect their daily life. Side effects such as fatigue, pain, muscle weakness, peripheral neuropathy, cardiovascular and pulmonary complications, endocrine changes, anaemia, immune dysfunction, sleep disorders, depression, anxiety, gastrointestinal disturbance and skin changes can develop during the treatment. The most common side effects during the treatment in patients with CRC are generalised and muscle weakness. In these patients, physical exercise programs improve the symptoms and side effects of chemotherapy, along with the quality of life^[5,74,75]. In the Cochrane study, which included 56 randomised trials involving patients with cancer-associated fatigue, exercise was found to decrease cancer-associated fatigue and improve depression and sleep disorders^[76]. The 6- and 12-wk home-based exercise programs, which are easier to apply, have been shown to significantly improve physical fitness in CRC survivors and to be effective and applicable in increasing the level of physical activity^[77,78]. The CASUS (Cancer Survivor Study), a prospective observational study investigating the effect of physical activity and nutrition on the quality of life and disease recurrence and survival in CRC survivors, is on-going^[79].

Patients with metastatic disease have very low participation rates in exercise programs. Prospective studies investigating the effect of exercise on clinical outcomes have shown that physical activity improves prognosis in patients with CRC even in advanced stage patients^[52]. In a study regarding patients with stage 4 CRC, an improvement in fatigue, functional capacity, sleep quality and the quality of life was reported in patients after 8 weeks of home-based exercise programs^[80]. Moreover, low

Table 1 Ongoing trials on colorectal cancer and exercise

Study	Conditions	Interventions	Title	Status
NCT01325909	Rectal cancer	Exercise programme	Exercise training in colorectal cancer patients	Completed
NCT03515356	Colorectal cancer	Motivational interviewing-walk intervention/physical activity education pamphlet	Exercise to reduce chemotherapy-induced peripheral neuropathy	Recruiting
NCT01924897	Colorectal cancer	Exercise training	Preop cardiopulmonary exercise testing and exercise training in colorectal patients	Unknown
NCT00985400	Colorectal cancer	Exercise programme/telephone-based intervention	Doctor-recommended home-based exercise program or relaxation training in improving physical function and controlling symptoms in patients with stage IV or recurrent colon cancer that cannot be removed by surgery	Active,not recruiting
NCT00230646	Colon cancer/rectal cancer	Exercise counseling	Promoting physical activity after colorectal cancer	Completed
NCT01133132	Colon cancer	Survivorship CHESS (mobile comprehensive health enhancement support system)	Interactive cancer communication system directed physical activity enhancement for colon cancer survivors	Completed
NCT02597075	Metastatic colorectal cancer	Standard therapy+physical activity program/standard therapy	Physical activity in patients with metastatic colorectal cancer who receive palliative first line chemotherapy	Recruiting
NCT02191969	Colorectal Cancer/fatigue	Walk with ease	Physical activity intervention for older patients during chemotherapy for colorectal cancer	Recruiting
NCT02966054	Colon cancer/rectal cancer	Digital health physical activity intervention group	Self-monitoring and reminder texts to increase physical activity after cancer:a pilot randomized controlled trial	Completed
NCT00373022	Colorectal Cancer/depression/anxiety disorder	Exercise programme	Moderate physical activity in helping patients recover physically and emotionally from stage II or stage III colorectal cancer	Completed
NCT01708824	Colorectal cancer	Physical activity/dietary	Diet and physical activity intervention in CRC survivors	Unknown
NCT03232814	Colorectal cancer	Group-based walking	Walk on:a community-based approach to increase physical activity among men treated for colorectal cancer	Withdrawn
NCT01991847	Colorectal cancer	Physical activity	Tertiary prevention by exercise in colorectal cancer therapy	Completed
NCT02056691	Colorectal cancer	Exercise programme/muscle biopsy	Exercise induced changes in colorectal cancer tissues	Completed
NCT00819208	Colorectal cancer/anxiety/depression/fatigue/sleep disorders	Exercise intervention	Health education materials with or without a physical activity program for patients who have undergone treatment for high risk stage II or stage III colon cancer	Recruiting
NCT02347852	Colorectal neoplasms	Regorafenib	Assessment of physical activity during therapy with regorafenib for metastatic colorectal cancer	Completed
NCT02780284	Colorectal cancer	Physical activity intervention	Microbiome, exercise tracking study	Unknown
NCT02250053	Colon cancer (stage 2 and 3)	Exercise	Exercise and colon cancer	Unknown

NCT03049124	Rectal cancer	Exercise	Exercise for adults diagnosed with rectal cancer	Recruiting
NCT03082495	Rectal cancer	Exercise	Exercise during and after neoadjuvant rectal cancer treatment	Recruiting
NCT03111823	Stage IV colorectal cancer	Exercise intervention	Exercise program during chemotherapy in metastatic colorectal cancer	Terminated
NCT00977613	Colorectal cancer	Exercise counseling	Adherence to a recommended exercise regimen in colorectal cancer patients	Completed
NCT03291951	Colon cancer	Resistance training	Focus on reducing dose-limiting toxicities in colon cancer with resistance exercise study	Enrolling
NCT02264496	Colorectal cancer	Exercise	Prospective randomised trial of exercise and/ prantioxidants in colorectal cancer patients undergoing surgery	Completed
NCT03120104	Rectal cancer	Pelvic floor muscle exercise	Physical exercise for colorectal cancer patients after transanal total mesorectal excision	Recruiting
NCT03186638	Colorectal cancer (stage 1-3)	Exercise intervention/ibuprofen	Exercise and low-dose ibuprofen for cognitive impairment in colorectal cancer patients receiving chemotherapy	Recruiting
NCT00668161	Colon cancer prevention	Exercise	Effect of exercise on biomarkers of colon cancer risk	Completed
NCT02538913	Rectal neoplasms	Exercise training	Exercise training for rectal cancer patients	Recruiting
NCT02724306	Colon polyps/adenomas	Active lifestyle programme	Physical activity intervention with people at increased risk of developing colon cancer	Completed
NCT01859442	Locally advanced rectal cancer	Structured responsive interval exercise training programme	The effects of cancer therapies and exercise on mitochondrial energetics and fitness	Completed
NCT01914068	Rectal cancer	Supervised exercise in hospital	The effects of a 9 wk exercise programme on fitness and quality of life in rectal cancer patients after chemoradiotherapy and before surgery	Completed
NCT02057991	Colorectal cancer/anxiety/depression/fatigue	Educational intervention/CAM exercise therapy (mindfulness exercise video)	Mindfulness-based exercise video in educating Hispanic/Latino patients with colorectal cancer and their caregivers	Terminated
NCT02403024	Colorectal cancer	Interval walking	Feasibility and Efficacy of Interval Walking in patients with colorectal cancer	Completed
NCT02188342	Colorectal cancer	High intensity interval training	Assessing the effectiveness of a preoperative high intensity interval training programme in older colorectal cancer patients	Completed
NCT03336229	Colorectal cancer	Exercise Intervention	Enhancing fitness with preoperative exercise in colorectal cancer surgery	Not yet recruiting
NCT02586701	Colorectal cancer	Supervised /non-supervised exercise	Supervised versus non-supervised exercise on adherence and functional outcomes in colorectal patients	Completed

NCT01210313	Colorectal cancer	Physical activity	Physical activity for reduction of recurrence rate after adjuvant chemotherapy for localised colorectal carcinoma	Completed
NCT02299596	Colorectal cancer	Physical activity	Physical activity in relation to surgical procedures	Recruiting
NCT03361150	Colorectal cancer	Physical activity	High-intensity interval <i>vs</i> moderate continuous training in surgical prehabilitation	Completed
NCT02889276	Colorectal cancer	Unsupervised activity/Functional resistance training	Effects of functional exercise on fitness and QoL in cancer survivors	Recruiting
NCT02895464	Colorectal cancer	Exercise	Feasibility of home-based preoperative exercise in older people	Completed
NCT02499939	Colorectal cancer	Exercise/ultrasound therapy	Ultrasound therapy and therapeutic exercise for chemotherapy induced peripheral neuropathy	Completed
NCT02522520	Colorectal cancer	Pedometer intervention	Pedometer Intervention and health effects for sedentary colorectal cancer patients during adjuvant chemotherapy	Recruiting
NCT02442583	Colorectal cancer	Brochure regarding sedentary behavior	Reducing sedentary behaviors among colorectal cancer survivors	Completed

intensity physical activities in patients with stage 4 metastatic cancer are recommended. The studies have shown no clear association between the physical activity and overall or CRC-specific survival in patients with metastatic CRC^[81,82].

The CALGB89803/ALLIANCE study, a prospective observational study, investigated the effect of physical activity on survival in patients with colon cancer before and after recurrence 6 months post-completion of adjuvant therapy. After adjusting the potential factors that can affect the survival, a statistically significant 29% improvement in mortality was observed in physically active patients with recurrent colon cancer^[83]. The physical activity prior to recurrence appears to be a factor that affects prognosis in patients with recurrent colon cancer.

OBSTACLES, CONTRAINDICATIONS AND COMPLICATIONS FOR EXERCISE

Although it is known that exercise has beneficial effects in patients with CRC and survivors, there are some obstacles to participation of patients in exercise regimens. Fatigue is the most frequently reported obstacle to exercise in patients with CRC^[84]. More than 60% of patients with cancer complain of weakness during and after treatment. Fatigue decreases the quality of life and physical activity. The cause of fatigue in patients with cancer is unknown, and may develop because of the disease itself or its treatment. Furthermore, it may occur because of other clinical issues such as depression, physical inactivity and sleep disorders. Although complaints such as nausea and pain can be treated effectively during cancer treatment, effective treatment for fatigue is yet unavailable. After treatment, fatigue decreases over time; however, 30% of the patients may continue to complain for years^[85]. In addition, treatment-related side effects and comorbid conditions (cardiopulmonary disease and diabetes) may be an obstacle to exercise. CRC survivors with peripheral neuropathy have been shown to participate in lesser physical activity than those without neuropathy^[86].

In addition to the effect of exercise on survival, several studies have evaluated the efficacy and reliability of physical activity applications (home-based, supervised and telephone-based counselling and interval walking) in CRC survivors. These studies have shown that aerobic and resistance exercises were safe and did not increase the risk of side effects throughout the chemotherapy^[80,87-89].

Understanding the factors that impede exercise practices is important for directing patients with cancer to the appropriate exercise programs. However, data regarding the appropriate exercise dose and type to safely correct the results is insufficient. Guidelines should be developed according to each patient's disease, age and

comorbid condition. Clinicians can influence patients by encouraging them to exercise, thereby increasing patient participation in physical activity. However, in a study investigating the effect of oncologists' exercise advice on patients, oncologists' exercise re-recommendations alone were shown to be insufficient to increase participation in exercise. Reportedly, exercise package programs may be ideal for increasing the exercise participation^[90].

Contraindications for exercise are heart failure, acute infectious disease, metabolic disease (thyrotoxicosis and myxoedema) and mental and physical disorders^[91]. Non-scheduled exercises can cause complications. Furthermore, intense physical activity, particularly in the early period, can result in deterioration of wound healing and parastomal hernias. Skeleton stability should be investigated before exercise, if patients are suspected of bone metastasis. Blood counts should be monitored in patients who are scheduled to participate in exercise during chemotherapy. For intensive and light exercises, thrombocytes should be at least 50000/ μ L and 20000–50000/ μ L, respectively. If haemoglobin is ≤ 8 mg/dL, exercise may cause cardiac ischemic complications because of increased O₂ requirement. Neutropenia is not a contraindicated condition for exercise; however, caution should be exercised in terms of infection. Patients should avoid severe exercises because of the toxicity (nausea, vomiting, nephrotoxicity, cardiotoxicity and diarrhea) caused within 24 h of chemotherapy^[24]. Severe peripheral neuropathies constitute the contraindications for exercises. Physical activity studies have reported no side effects because of exercise during and after cancer treatment^[91].

EXERCISE AND MECHANISMS OF ACTION

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 and adiponectin)], oxidative stress and inflammation and impaired immune function^[42,92] (Figure 1).

Insulin pathway

Insulin influences DNA synthesis, cell survival, proliferation and differentiation using various cellular signalling pathways via insulin growth factor receptor IGF1R^[93]. Elevated systemic IGF1 levels are associated with CRC risk^[94]. In preclinical studies, exposure to insulin has been shown to induce colonic tumour cell development^[95–97]. Moreover, observational studies have supported pre-clinical studies^[98,99]. Insulin resistance is associated with higher CRC incidence and mortality^[100]. In the studies, the degree of IGF1R over-expression has been shown to be correlated with the tumour stage in CRCs^[101].

Physical activity decreases insulin resistance and the insulin levels affecting the IGF pathway and indirectly decreases the risk of CRC, recurrence and mortality. With regard to the IGF pathway, heterogeneity is observed in response to exercise. In some studies, an increase in IGF-1 and IGFBP-3 levels was observed with exercise, whereas in some cases, a decrease was observed. This clinical condition may be because of several factors affecting the association between the IGF pathway and exercise^[102]. Despite heterogeneous results, decreased IGF-1 levels and increased IGFBP-3 levels may be a reasonable mechanism underlying the inverse correlation between CRC and physical activity^[103]. The association between exercise and CRC cannot be explained using a single mechanism because exercise and interrelated factors exert varying effects.

Inflammation

Inflammation is known to be a risk factor for various chronic diseases (obesity and metabolic syndrome) including cancer. Inflammation plays an important role in cancer development and progression^[104]. Although the underlying mechanisms are yet unclear, the inflammatory process appears to be an important pathway associated with the risk of CRC. Physical activity can decrease systemic inflammation and improve immune function^[105]. Proinflammatory cytokines such as IL-6, C-reactive protein and tumour necrosis factor (TNF)- α are associated with an increased risk of cancer. Various studies have demonstrated the effects of physical activity on IL-6 in the colon cancer model. In a study conducted by Mehl *et al*^[106], a decrease in plasma IL-6 was observed in APC^{min/+} male mice after treadmill running. This result has been shown to be associated with fewer polyps.

New preclinical studies have shown that inflammation is associated with polyp

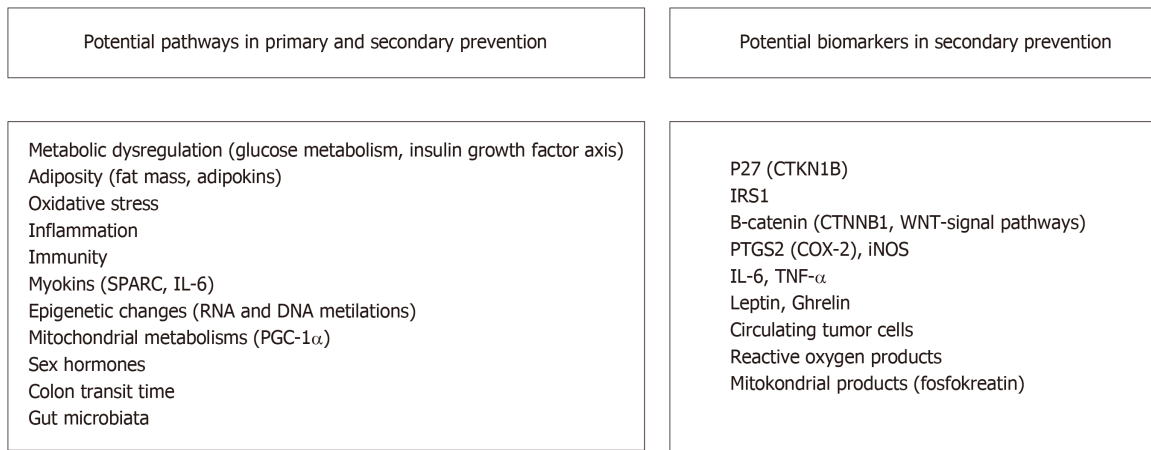


Figure 1 Biological potential pathways as explanatory mechanisms of the association between physical activity and primary and secondary prevention of colorectal cancer/potential biomarkers in secondary prevention. SPARC: Secretory protein acidic and rich in cysteine; PGC-1 α : Peroxisome proliferator-activated receptor gamma co-activator 1 α ; CTKN1B: Cyclin-dependent kinase inhibitor 1B; IRS1: Insulin receptor substrate 1; CTNNB1: Catenin beta 1; PTGS2: Prostaglandin-endoperoxide synthase 2; COX-2: Cyclooxygenase-2; TNF- α : Tumor necrosis factor alpha; iNOS: Inducible nitric oxide synthase.

formation and progression and that the cyclooxygenase isoenzymes (COX-1 and -2) particularly play an important role in intestinal tumour formation^[103]. Administration of nonsteroidal anti-inflammatory drugs that inhibit the COX enzyme is known to be associated with a decreased risk of colon cancer (RR: 0.60, 95%CI: 0.40–0.89)^[107,108]. Physical activity results in a local anti-inflammatory effect by decreasing COX-2 and iNOS (inducible nitric oxide synthase) expression in the colon mucosa. Adipocyte, energy balance, insulin, adipokines, estrogen and other factors known to play a role in carcinogenesis have been shown to affect the inflammatory response. Therefore, these factors may be involved in the indirect effect of physical activity on inflammatory processes in cancer^[108,109].

Myokines

Myokine secretion from the skeletal muscles may be involved in the protective effect of exercise. Studies have shown that exercise-induced myokines include IL-6, IL-8, IL-15, brain neurotrophic factor and leukaemia inhibitory factor released from the muscle fibres. Exercise enhances the insulin sensitivity through these cytokines and decreases the production of proinflammatory cytokines^[110-112].

Recent studies have shown that the secretory protein acidic and rich in cysteine (SPARC protein), a cellular matrix protein known as a myokine, is released from the muscle tissue after exercise and is involved in intercellular interaction and cell differentiation. The SPARC protein forms a biological association between colon tumorigenesis and physical activity. The SPARC protein prevents CRC development by increasing apoptosis^[113]. In a study conducted by Aoi *et al*^[114], the antiproliferative and proapoptotic effects of the SPARC protein in colon cancer cells has been shown.

Immunity

The mechanisms underlying the protective effect of exercise on the risk of colon cancer are complex. The role of exercise in the immune system in cancer prevention is yet unclear. Recently, macrophages and T cells have been the important factors in colon cancer pathogenesis. Accumulation of intra-tumoral macrophages is associated with poor prognosis in colon cancer^[115,116]. Exercise-induced changes in the immune system are a possible mechanism. In a preclinical study, exercise was shown to affect the immune cell parameters in the mucosal tissue of APC^{min/+} mice. Exercise decreased the expression of macrophage and regulatory T-cell markers and increased the number of cytotoxic T-cells^[117]. Other preclinical studies confirmed that exercise was particularly influenced immune cells such as T lymphocytes and macrophages^[118,119]. Furthermore, exercise may have a positive effect on immune aging^[120]. Exercise has been shown to increase natural killer cell cytotoxicity, monocyte and macrophage number and function and the CD8 T-cell ratio. Furthermore, it has been shown to decrease the increased antigen presentation, inflammation and number of proinflammatory monocytes and prevent the accumulation of aged T-cells^[121-123]. These mechanisms demonstrate the complexity of interaction between the risk of cancer and physical activity. Further studies are required to fully understand the associations among immunity, exercise and cancer.

Other mechanisms

In CRC, there are other suggested mechanisms (micro RNA, global DNA methylation, intestinal microbiota, colon transit time and mitochondrial dysfunction) underlying the effects of exercise on tumorigenesis. In recent years, it has been suggested that intestinal microbiota is associated with CRC incidence and progression and may predict the response to immunotherapy. Diet and lifestyle changes alter the intestinal microbiota^[124,125]. Several studies have shown that some gut microbes such as anaerobic bacteria significantly increased in patients with CRC; however, further investigation is required to assess the importance of these bacteria and their metabolites in CRC pathogenesis. Moreover, the effect of lifestyle on the anticancer immune response is yet unclear^[126].

Another mechanism that explains the association between exercise and CRC is that the exercise decreases the colon transit time. Thus, the interaction of intra-colonic chemicals with colonic mucosa is limited^[127]. Moreover, CRC development and risk factors such as obesity and aging are associated with mitochondrial dysfunction. In a recent study, it was shown that the peroxisome proliferator-activated receptor gamma co-activator 1 α (PGC-1 α), the major regulator of mitochondrial functions, may be a biomarker involved in the protective effect of physical activity in patients with CRC^[128].

BIOMARKERS AND THE EFFECT OF EXERCISE ON PATIENTS WITH CRC

Physical activity before and after the diagnosis in CRC is associated with improved disease outcomes and decreased risk of recurrence; however, the underlying molecular mechanisms are unknown. Various observational studies have focused on whether the different molecular properties of CRC affect the association between physical activity and survival. As observed in the standard oncology treatments, every treatment does not have the same effect on every patient. Similarly, physical activity should not be expected to benefit all patients. The molecular basis of the association between CRC and physical activity must be highlighted, and tumour biomarkers or patient characteristics that can predict the response to exercise must be identified. Using molecular markers and protein expression, a patient subgroup that can benefit the most from physical activity can be determined (Figure 1).

P27

P27 loss is common in CRC. P27 is a cyclin-dependent kinase inhibitor that is additionally associated with the insulin pathway. High insulin and IGF-1 levels result in P27 downregulation. In response to energy restriction and physical activity, P27 expression increases^[59]. High P27 (CTKN1B) levels are associated with cell cycle termination^[129]. The benefit of physical activity may be affected by tumour P27 status. In a preclinical study, patients with colorectal tumours that expressed P27 experienced greater benefit from physical activity after diagnosis than those with a P27 loss. People with ≥ 18 met h/week of physical activity after diagnosis showed a 67% decrease in colon cancer-specific mortality compared with less active subjects. No statistically significant association was observed between the patients with tumour and loss of P27^[59].

B-catenin

The B-catenin (WNT) signalling pathway plays an important role in CRC development, energy metabolism, adipogenesis, obesity and metabolic diseases. The activation of the WNT signalling pathway because of a loss of APC and its major mediator CTNNB1 (B-catenin) results in cell growth independent of the energy balance^[130]. Physical activity alters the WNT-CTNNB1 signal in the mouse colonic mucosa and the WNT-CTNNB1 signalling pathway affects the cellular sensitivity to physical activity^[131].

In one study, patients with early-stage CRC with CTNNB1-negative tumours, who had ≥ 18 met hour/week of physical activity after diagnosis, showed a 67% decrease in the risk of CRC-specific mortality compared with that in inactive patients. However, no correlation was observed in CTNNB1-positive patients^[60]. In a study evaluating whether B-catenin predicted the benefit of exercise in patients with metastatic colon cancer receiving chemotherapy, it was found that exercise did not affect the survival (HR: 0.98, 95%CI: 0.32–2.97). However, patients with weak staining for B-catenin in the exercise program had a lower mortality rate (HR: 0.39, 95%CI: 0.025–6.1)^[132]. In clinical practice, CTNNB1 status can be used as a predictive biomarker in response to exercise applications^[133].

PTGS2 (COX-2) and TNF- α

Physical activity can affect inflammation-induced cell growth. In preclinical studies, exercise has been shown to alter chemically induced COX-2 (cyclooxygenase-2) expression and cell proliferation in the colon. CRC-specific survival may vary based on the PTGS2 (prostaglandin-endoperoxide synthase 2/COX-2) expression status^[134]. Among 382 patients with PTGS2 (COX-2)-positive CRC, those with the highest physical activity had an 82% decreased CRC-specific mortality compared with the least active patients. However, the protective effect was not observed in 223 patients with PTGS2-negative CRC^[61]. High TNF- α expression in colon tumour tissue is associated with positive lymph node stage and colon cancer recurrence^[135]. In patients with colon cancer, the circulating TNF-alpha levels were observed to be decreased by exercise^[88].

Insulin, IGF-1 and IRS1

Diabetic patients and patients with metabolic syndrome have an increased risk of CRC recurrence^[136]. In addition, increased insulin and IGF-1 levels in patients with CRC are associated with a poor prognosis^[137]. In one study, postoperative physical activity in CRC survivors decreased insulin levels and insulin resistance and increased IGF-1 (17.8%, P : 0.007) and IGFBP-3 (30.3%, P : 0.0013) levels^[88]. However, the decrease in insulin and IGF levels is known to decrease the risk of CRC and improve survival outcomes^[104].

Insulin receptor substrate 1 (IRS1), insulin and IGF are mediators in the insulin signalling pathway, and downregulation of IRS1 is associated with insulin resistance^[138]. In a study evaluating 371 patients with stage 1–3 CRC, post-diagnostic physical activity significantly improved the CRC-specific survival in patients with low IRS1-expressing tumours, with a hazard ratio (HR) of 0.15 (95% CI: 0.02–1.38) in the IRS1-negative group, 0.45 (95% CI: 0.19–1.03) in IRS1-low group and 1.32 (95% CI: 0.50–3.53) in IRS1-high group. If confirmed by other studies, it may be used as a predictive marker to identify the patient groups that will benefit the most from exercise^[62].

Leptin and Ghrelin

Preclinical studies have shown that exposure of colon cancer cells to adipocytes and pre-adipocytes increases cell proliferation^[139]. Exercise decreases visceral obesity. Physical activity and exercise decrease inflammatory adipocytes and increase anti-inflammatory adipokines^[140]. Leptin and ghrelin are important regulating hormones in the intake and consumption of energy and weight control. Decreased body fat mass and percentage is associated with an increase in ghrelin levels^[141]. Ghrelin was found to be associated with increased proliferation and invasion in CRC by endogenous and autocrine effects^[142]. The endocrine and autocrine effects of ghrelin in CRC vary. Aerobic exercise causes a decrease in leptin and an increase in ghrelin^[143,144]. In one study, because of the increase in adipose tissue, a decrease in ghrelin levels and an increase in the risk of colon cancer were determined^[145]. In a study evaluating the effect of 8 weeks of exercise on plasma leptin and ghrelin levels in patients with CRC, a significant increase in ghrelin levels was observed in the exercise group after 8 wk. Plasma leptin levels and insulin resistance did not differ significantly. Plasma ghrelin levels were negatively correlated with the body fat percentage. If confirmed by other studies, ghrelin hormones can be used as biomarkers to demonstrate the benefit of exercise.

Other biomarkers

Genetic and epigenetic changes induced by reactive oxygen products may contribute to CRC progression. Chronic exercise may decrease the risk of recurrence by decreasing the systemic oxidative stress^[146,147].

Circulating tumour cells predict stage 1–3 colon cancer recurrence and mortality^[148]. In a study, patients with stage 1–3 colon cancer were randomised into two groups and were subjected to aerobic exercise for 150 min/wk and aerobic exercise for 300 min/wk for 6 mo. After 6 mo, a significant decrease was observed in tumour cells circulating in both low- and high-dose exercise arms. However, no exercise dose-response association was observed^[149]. The mechanism underlying the effect of exercise against the circulating tumour cells is yet unknown.

In a recent study, it was observed that the central carbon metabolism was affected, and a significant decrease in phosphocreatine levels was observed in the tumour models that responded to exercise. This finding indicates a change in tumour energy metabolism after exercise in CRC. Furthermore, this study showed that the underlying mechanism of exercise benefit may be the modifications in tumour cell mitochondrial metabolism^[150]. Aerobic exercise has been shown to be effective through various intra-tumoral and systemic mechanisms in cancer onset, progression

and metastasis. Furthermore, exercise can activate different biological mechanisms at different intensities^[151].

EXERCISE AND GUIDELINES

The ACS and ACSM have developed physical activity and dietary guidelines for patients with cancer. To recommend specific exercise programs, the patient's comorbid conditions and exercise contraindications should be carefully evaluated through medical screening. In addition, the patient's age, gender, type of cancer treatment and physical performance should be considered. Echocardiography should be performed in patients who have a history of cardiac disease or a cardiotoxic chemotherapy regimen. Patients with a history of severe smoking and suspected pulmonary dysfunction should undergo a respiratory function test^[24]. If no contraindications (presence of widespread lytic bone metastases, severe thrombocytopenia, anaemia, fever or presence of active infection or safety issues) are present, it is advisable to offer moderate personalised aerobic exercise programs for most patients. Exercise programs vary according to the type, intensity and frequency of exercise^[152]. For colon cancer survivors, supervised exercise is an appropriate program^[153]. In patients with advanced cancer, the applicability of exercise programs is limited.

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. For adult patients with cancer who have fatigue, the American Society of Clinical Oncology manual recommends 150 min/wk of moderate aerobic exercise (fast walking, cycling or stretching) and two or three power-boosting exercises (weight lifting)^[154].

Recommendation of the 2012 ACS guideline: It is recommended to avoid inactivity and to return to normal daily activity immediately after diagnosis, aiming for at least 150 min/wk of moderate or 75 min/wk of vigorous aerobic exercise, including exercises that require strength at least 2 d/wk^[36]. However, it is recommended that this amount must be increased to 225 min (45 min/d, 5 d/wk) in appropriate patients. All patients with cancer should be encouraged to participate in regular physical activity during their lifetime.

CONCLUSION

In recent years, various studies have been conducted regarding the effect of exercise on cancer prevention and clinical outcomes. Increasing observational and experimental evidence suggests that exercise can modify the biology of CRC. Based on the results of the study, lifestyle interventions that provide an improvement in diet and exercise are recommended as an effective method to prevent CRC and improve the negative effects of cancer and its treatment. However, the required exercise dose, type and intensity are yet unclear. The results of randomised prospective studies are expected to determine the optimal amount of exercise, type and intensity and develop the most appropriate exercise plan according to the requirements and comorbidities of the patients and eventually formulate more useful guidelines. In this review, we outlined the beneficial effects of exercise in the prevention and treatment of CRC and the potential biological mechanisms underlying these beneficial effects.

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