

# Exercise and Colon Cancer: Primary and Secondary Prevention

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Many studies have demonstrated the effects of exercise on both primary and secondary prevention of colon cancer. Exercise appears to have a dose-response reduction in the rate of colon cancer. The mechanism by which exercise provides this benefit is not known, but increase in insulin-like growth factor-binding protein and reduction of prostaglandins appear to be the likely cause. Once a person develops colon cancer the benefits of exercise appear to continue both by increasing quality of life and reducing cancer-specific and overall mortality.

## Introduction

Exercise is associated with many health benefits [1], including prevention of coronary artery disease, diabetes, and many other diseases. The effects of exercise on the formation of colon cancer are explored in this article. The reduction in risk of colon cancer, how exercise decreases the incidence of colon cancer, and the effects of exercise after the diagnosis of colon cancer are explored. The amount of exercise needed to reduce colon cancer is becoming better understood since the early studies of the 1980s. How exercise provides this protective effect is uncertain. A number of proposed mechanisms are explored, including insulin-like growth factor (IGF)-1, prostaglandins, water intake, and transit time. When cancer is found, whether exercise can help prevent recurrence and increase quality of life is better understood through two recent studies on the topic. The importance of daily exercise in many illnesses, in addition to both primary and secondary colon cancer prevention, is becoming more obvious.

## Colon Cancer and Exercise

Recently there has been great interest in the relationship between physical activity and reduction of cancer incidence. Colon cancer reduction is no exception. Clear correlations have been found between exercise and the reduction of colon cancer incidence [2,3]. The correlation of exercise and colon cancer has been found in studies involving a diverse population from different continents and diverse ethnic groups. There is a clear pattern that shows that men who are physically active have a reduced risk of colon cancer [3]. The median risk reduction for men is between 30% and 40% [1]. Results of studies involving women have had mixed results [3], with an estimated benefit of between 10% and 20%. Despite mixed results in women, it appears that colon cancer risk is reduced for physically active people regardless of sex. The benefits of exercise are also greater in the right colon than the left [4].

The amount of exercise needed to produce a reduction in colon cancer rates has recently become better understood. Recent studies show that exercise has an effect on colon cancer rates in a dose-related response; higher levels of activity lead to greater declines in cancer rates [3,5,6]. The difficulty with most of the studies on the effect of exercise on colon cancer, as pointed out by a recent meta-analysis [1], is the variation in the methods of measuring type of exercise, intensity, duration, and frequency of exercise. What can be concluded from the current research is that moderate to high levels of weekly physical activity are needed for a reduction in cancer risk [1,3,7••].

There are two large studies of note that investigate dose-related responses of exercise on colon cancer rate reduction [5,6]. The Harvard Alumni Study [5] followed 17,148 men for a maximum of 26 years. During the study, 225 men developed colon cancer. The men who participated in physical activity equivalent to at least 30 minutes per day, 5 days per week, had a 50% reduction in colon cancer rates compared with men who were sedentary. Physical activity was defined in this study as both the time set aside for daily exercise, as well as other daily physical activities such as climbing stairs [5]. The Nurses Health Study [6] followed more than 67,000 women over 6 years; 212 women developed colon cancer during the study

period. Women who participated in 4 hours of exercise per week showed a 33% risk reduction for colon cancer. Those who exercised more than 5 hours per week showed a reduction of 46% [6]. The physical activity level in the Nurses Health Study was defined as exercise and recreational activity but not ordinary daily activities.

These studies show an obvious correlation between exercise and a reduction in colon cancer rates. A weakness in both studies is that they utilized retrospective recollection of activity levels, making it difficult to conclude exactly how much exercise is necessary to reduce the risk of colon cancer. Consistent with the Nurses Health Study, a recent prospective study showed that about 4 hours of exercise per week reduced precursor markers of colon cancer in active subjects as compared with sedentary subjects [8•]. The effect of exercise appears to be significant at levels greater than approximately 4 hours of activity per week [7••]. The level may be less in male subjects, as seen in the Harvard Alumni Study. The amount of activity needs to be moderate to high (at least 30 min per day); the level of activity is defined in different manners. The type of physical activity in the studies can be leisure time activity (gardening, hobbies), regular physical activity (planned exercise, sports), or daily occupational activity. More work is needed to better define the type of activity, including intensity, which provides the optimal benefit.

### Protective Mechanisms of Exercise

The mechanism by which exercise lowers the rate of colon cancer has been speculated by a number of investigators. These include IGF-1/insulin-like growth factor-binding protein (IGFBP), the amount of water intake, reduction in inflammatory markers, decrease in fecal transit time through the colon, and other less well-defined mechanisms. The definitive mechanism or mixture of mechanisms is not clearly understood.

IGF-1 has been studied as a potential cause in colon cancer because of its link to other types of cancer. It has been proposed that increased levels of IGF-1 correlate with increased colon cancer rates [9,10]. For example, people with acromegaly have high circulating levels of IGF-1 and elevated rates of colon cancer [11].

IGF-1 in animal models and in vitro studies plays an important role in tumor development, angiogenesis, and tumor metastasis [12,13]. Chronic exercise decreases IGF-1 elevation over time [14]. Aerobic exercise increases IGFBP levels [14]. Similarly, increases in IGFBP are found with 9 months of twice-weekly strength training [15]. IGFBP affects the bioavailability of IGF-1, higher IGFBP limits the effect of IGF-1. Exercise may diminish colon cancer by increasing IGFBP and limiting the effects of IGF-1 on the colon mucosa.

Water intake is another possible mechanism for why exercise reduces the rate of colon cancer. Water is theorized to soften the gut contents, decrease the transit time, and

dilute potential carcinogens [16]. People who participate in physical activity are believed to have increased water intake throughout the day. Leiper et al. [17] reported fluid intake was greater among men who exercise regularly than sedentary men. Studies support water intake and reduction in colon cancer. Women who drink more than five glasses of water per day had a lower incidence of colon cancer when compared with those who drank less than two glasses per day [18]. This same study showed only a marginal association with reduction in colon cancer in men who drink more than four glasses of water per day versus those who drink only one glass of water daily. Murtaugh et al. [19] demonstrated an association between water intake and reduction of rectal cancer. The effect of water intake and physical activity may, however, be independent factors, as reported Tang et al. [16] in their case-control retrospective study that showed that water intake was independent of physical activity for reduction in colon cancer risk. Therefore, people who exercise may have the dual benefit of increased water intake and IGF-1 reduction.

Prostaglandin production and the formation of colon cancer have been linked [20]. The use of nonsteroidal anti-inflammatory drugs has been shown to reduce the rate of colon cancer [21•,22]. Exercise similarly can reduce the production of prostaglandins in the body. Martinez et al. [23] found a 28% reduction of prostaglandins in people who jog 30 minutes or walked 1 hour per day. Exercise programs appear to decrease the production of pro-inflammatory markers [23]. Therefore, the effect of exercise on colon cancer may be secondary to the reduction of prostaglandin formation.

Colon transit time may have an effect on colon cancer. Theoretically, a decreased colon transit time means decreased exposure of possible carcinogens to the colon mucosa. Studies of the effects of exercise on colonic transit time have demonstrated mixed results [24–26]. Studies have found no association between transit time and colon cancer [27,28]. Though transit time is theorized as a reason for reduction in colon cancer, the evidence is not supportive of this theory.

The mechanism by which exercise reduces the risk of colon cancer is not certain, but the reduction of IGF-1 bioavailability and/or the reduction of prostaglandins are supported by current literature. Water intake may play a role independent of exercise. Decreased transit time is postulated but not supported by the literature. Regardless of the exact mechanism, exercise appears to help reduce the risk of developing colon cancer and should be recommended to patients as a method of preventing colon cancer.

### Physical Activity/Exercise and Patients Diagnosed with Colon Cancer Should cancer patients exercise?

The American Cancer Society recommends physical activity as a part of the care of patients with cancer [29].

**Table 1. American Cancer Society expert committee grading of benefit in colorectal cancer**

Effect of increasing physical activity	Cancer recurrence	Overall survival	Quality of life
During treatment	Insufficient data	Possible benefit	Probable benefit
Post-treatment	Possible benefit	Probable benefit	Probable benefit

(Adapted from Brown et al. [34].)

A person diagnosed with colon cancer is more likely to make lifestyle changes including increasing physical activity than a person not diagnosed with cancer [30]. Research suggests that exercise may be an effective intervention for enhancing quality of life (QOL) in cancer survivors [31]. How physical activity affects survival from cancer is uncertain, but physical activity might improve prognosis of survival through the beneficial effects on cancer biomarkers and weight reduction [32,33]. Decreasing the risk for cardiovascular disease [32,33], a frequent cause of premature death for many cancer survivors [33], is another important benefit of increased physical activity. Physical activity improves cardiorespiratory fitness during and after cancer treatment, decreases subjective symptoms and physiologic effects during treatment, and increases energy levels after treatment [32]. Increasing physical activity appears to be beneficial and safe in the majority of colon cancer survivors [34].

#### Exercise and colon cancer treatment

Exercise is becoming an important component of cancer rehabilitation programs. A consistent finding across studies is that patients experience improved physical fitness and reduced fatigue [33]. Exercising during chemotherapy can be difficult. One study examined self-reported short-term exercise adherence following a 6-week supervised exercise program in a heterogeneous group of 61 cancer patients [35]. Even though there was a significant postprogram reduction in physical activity among participants, this level of activity was still higher than their baseline levels. Investigators recommended that a continuous supervised program may be required during chemotherapy, as the largest reduction in physical activity was found in those still receiving treatment.

Mustian et al. [36] reported on a nationwide population sample ( $N = 749$ ) on exercise participation during and within 6 months after chemotherapy and radiation therapy, the association of exercise with treatment side effects, and the communication between physicians and patients about exercise. Results demonstrated that exercise was associated with less severe side effects during and after treatment ( $P \leq 0.050$ ). Patients were more likely to continue to exercise if their physician discussed exercise with them. They concluded that cancer patients appear amenable to attempting exercise during and within 6 months after treatment.

A study that examined the effects of aerobic exercise on physiologic and psychologic function in patients rehabilitating from cancer treatment showed that low-

and moderate-intensity aerobic exercise programs were equally effective in improving physiologic and psychologic function in this population of cancer survivors [37]. Aerobic exercise appeared to be a valuable and well-tolerated component of the cancer rehabilitation process.

Patients being treated for colon cancer have decreased QOL, mostly due to treatment side effects [38]. Increasing QOL with exercise after being diagnosed with cancer appears to show positive correlation [36,38]. The amount and frequency of physical activity needed to improve QOL has not been fully defined.

The optimal amount of exercise during colon cancer treatment is not yet known. Information from studies on cancer in general demonstrates an increased QOL and reduction of cardiac risk factors with exercise during cancer treatment. The American Cancer Society states that there are insufficient data to conclude a benefit for starting an exercise program in preventing recurrence of cancer during cancer treatment, but they do propose a probable benefit of increased QOL from exercise started or continued during treatment (Table 1).

#### Cancer Recurrence/Survival

Evidence regarding the ability of exercise to prevent recurrence of colon cancer or increase survival is lacking. A systematic review [39] of physical activity and energy expenditure in exercise interventions following cancer diagnosis found no studies examining the effect of physical activity on cancer recurrence or survival. Overall, studies consistently demonstrated that physical activity has a positive effect on psychosocial processes, including fatigue and nausea. The conclusion of this review was that further work is needed to identify a dose-response effect of increased physical activity on cancer recurrence and survival.

Two recent studies demonstrate a positive effect of exercise on colon cancer survival and decreasing recurrence. The Melbourne Collaborative Cohort Study [40] followed colon cancer survivors for a median of 5.6 years. Patients who were physically active demonstrated an increase in IGFBP-3 of 26.2 nmol/L and a 48% reduction in colorectal cancer specific deaths (adjusted HR 0.52 [95% CI, 0.33–0.83];  $P = 0.006$ ). No association was seen for IGF-1 (adjusted HR 0.90 [95% CI, 0.55–1.45];  $P = 0.65$ ). The study supports the hypothesis that physical activity reduces the mortality rate of those diagnosed with colon cancer.

A recent prospective observational study looked at the influence of physical activity on the reduction of cancer

recurrence/survival in patients with colon cancer over a 3-year span [41]. The study group included 832 patients with Stage III colon cancer. Metabolic equivalent task (MET) score for physical activity assessment was measured. Physical activity after diagnosis of stage III colon cancer was associated with a significant reduction in cancer recurrence and overall mortality. Patients who engaged in at least 18 MET-hours per week of physical activity showed a better outcome, with 47% having significant improvement in disease-free survival.

Another study [42••] has demonstrated that recreational physical activity after the diagnosis of stage I-III colorectal cancer reduces the risk of cancer-specific and overall mortality. Women who engaged in 18 MET-hours per week had an adjusted hazard ratio for overall mortality of 0.43 (95% CI, 0.25–0.74) and a cancer-specific mortality of 0.39 (95% CI, 0.18–0.82). Increasing levels of exercise was strongly positive for both cancer-specific and overall mortality.

These new studies are very supportive for recommending exercise to patients who have had colon cancer for reduction of both cancer-specific and overall mortality prevention. A randomized controlled trial measuring short- and long-term impact of physical activity on cancer recurrence and survival is needed to help verify these results, as well as, quantify the amount of exercise to recommend.

## Conclusions

Exercise appears to have a dose-response in the reduction of colon cancer. The benefit is demonstrated with greater than 4 hours of exercise per week. The type of exercise needed (aerobic, strength training) has not been fully determined. Further studies are needed on the intensity level of exercise needed. The mechanism by which exercise reduces colon cancer risk appears to involve IGF-1/IGFBP as well as reduction in prostaglandins.

Exercise during and after colon cancer treatment probably benefits overall survival and quality of life. The initiation of exercise during cancer treatment is not well studied for colon cancer. There is recent evidence that QOL, cancer-specific mortality and overall mortality are improved with exercise after colon cancer is diagnosed. Exercise is beneficial to patients for both primary and secondary prevention of colon cancer.

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