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REVIEWS

Physical activity in colorectal cancer

Activitatea fizică în cancerul colorectal

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Abstract

Extensive epidemiological and experimental investigations have linked lifestyle and environmental factors to the risk of colorectal neoplasia. Protective factors include: a balanced diet based on whole grains, non-starchy vegetables and dairy products, maintenance of a healthy weight and regular physical activity, while excessive intake of red and processed meat, alcohol consumption and a sedentary behavior are frequently associated with carcinogenesis. These lifestyle factors are equally important even after a diagnosis of colorectal cancer. Both diet and physical activity can boost physical and physiological function, enhance the quality of life and reduce mortality among oncologic patients. The aim of this paper is to present the most relevant biological mechanisms linking physical activity with colorectal cancer in the context of prevention and cancer outcomes. Furthermore, we emphasize the importance of physical activity alone or in association with other modifiable lifestyle factors, as a reliable tool for prevention and/or improved prognosis in diagnosed patients.

Keywords: colorectal cancer, physical activity, prevention, prognosis, quality of life

Rezumat

Studiile epidemiologice alături de cercetările experimentale au evidențiat de-a lungul timpului importanța elementelor stilului de viață și a factorilor de mediu în cancerul colorectal. Cei mai importanți factori care conferă protecție includ o dietă sănătoasă bazată pe consum de cereale integrale, legume fără amidon și produse lactate, alături de menținerea unui indice de masă corporală normal și practicarea cu regularitate a activității fizice. Pe de altă parte, consumul excesiv de carne roșie și carne procesată, alcool și o viață sedentară contribuie la carcinogeneză. Acești factori sunt la fel de importanți și după diagnosticul de cancer colorectal. Atât dieta cât și activitatea fizică ajută la îmbunătățirea funcțiilor fizice și cognitive, îmbunătățesc calitatea vieții și contribuie la reducerea mortalității în rândul pacienților oncologici. Scopul acestei lucrări este de a prezenta cele mai relevante mecanisme biologice care explică măcar parțial efectele benefice ale activității fizice în prevenție și prognostic. În plus, în această lucrare de sinteză vom evidenția importanța activității fizice, ca factor singular sau în combinație cu alți factori ai stilului de viață, ca fiind un instrument important în prevenție și/sau în îmbunătățirea prognosticului la pacienții diagnosticați.

Cuvinte cheie: cancer colorectal, activitate fizică, prevenție, prognostic, calitatea vieții

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Introduction

Worldwide, colorectal cancer (CRC) is the third most diagnosed type of cancer among men and the second most frequently diagnosed cancer in women. Incidence is higher in more industrialized countries and trends are on the rise in Asia and Eastern Europe, especially in regions marked by a recent transition to a Western lifestyle. As for mortality, rates have decreased in most developed countries due to efficient screening and improved treatment (Ferlay et al., 2014); (1). However, in Eastern European countries, including Romania, mortality rates continue to grow and may reflect diagnosis in advanced stages and poorer response to treatment (2).

The etiology of CRC is multifactorial, including both hereditary conditions and lifestyle factors (Gryfe, 2009; Yamagishi et al., 2016); (3). There is strong evidence that consuming whole grains, foods containing dietary fiber and dairy products decreases the risk of colorectal cancer. Likewise, maintaining a healthy weight and being physically active is equally important. In addition, high intake of red and processed meat and drinking more than two alcoholic beverages per day was associated with increased risk (Schwingshackl et al., 2018; Tantamango et al., 2011); (3). Furthermore, these lifestyle factors are relevant even after a diagnosis of colorectal cancer and are associated with an improved quality of life and a reduced risk of recurrence or mortality (Van Blarigan et al., 2018; Van Vulpen et al., 2016; Lee et al., 2018a).

Physical activity as defined by the World Health Organization (WHO) refers to "any bodily movement produced by skeletal muscles that requires energy expenditure" (4). Regular physical activity in healthy individuals has highly recognized health benefits. Also, in the most recent paper by the World Cancer Research Fund, the panel of experts concluded that there is convincing evidence that physical activity of all types (occupational, household, transport and recreational) is associated with reduced risk of colon cancer. However, no conclusion was drawn for rectal cancer (3). Additionally, recent research points out that cancer patients and survivors who engage in regular physical activity experience an improved quality of life, have fewer chances of recurrence or onset of comorbidities, as well as reduced treatment-related side effects (Detroye et al., 2018; Van Vulpen et al., 2016). Several biological mechanisms have been postulated to support such beneficial outcomes, including changes in body composition, decreased insulin levels and insulin resistance and epigenetic modifications (Friedenreich et al., 2017; Schoenberg, 2016; Hughes et al., 2017). In this review, we present the most relevant biological mechanisms and pathways in relation to physical activity and colorectal cancer. We also highlight the importance of regular physical activity for prevention of colorectal carcinogenesis as well as for improved outcomes after diagnosis.

The mechanism of physical activity in colorectal cancer

CRC is a complex disease characterized by the accumulation of several genetic and epigenetic changes in epithelial cells that transform the normal colonic mucosa into adenocarcinoma (Hanahan & Weinberg, 2011; Yamagishi et al., 2016). It is widely acknowledged that genetic heritage is an important determinant of CRC risk. However, the majority of colorectal cancers occur sporadically as a result of epigenetic events mainly derived from exposure to environmental and lifestyle risk factors (Yamagishi et al., 2016; Fearon, 2011). The well-known lifestyle factors associated with colorectal cancer development include an unbalanced diet, smoking, alcohol intake, physical inactivity and being overweight or obese. Diet-related risk factors such as frequent consumption of red and processed meat, cooking meat at high temperature, as well as low intake of fruits, vegetables and whole grains have been associated with colorectal carcinogenesis, while a healthy diet reflected by a Mediterranean dietary pattern can protect from developing colorectal cancer (3). The most common strategies for prevention aim to change dietary habits. Likewise, physical activity represents an important modifiable lifestyle factor with reported benefits in primary prevention of colorectal cancer, as well as in improving prognosis and quality of life in cancer survivors (Van Vulpen et al., 2016; Lee et al., 2018a).

There are several proposed mechanisms by which physical activity can prevent colorectal cancer or improve the prognosis and quality of life of diagnosed patients. These mechanisms are not fully elucidated, although research advances over the past few years have generated useful insights. One proposed mechanism is related to counteracting obesity and the downstream cascade of negative effects. Obesity arises as a consequence of unhealthy eating habits and sedentary behavior, leading to a chronic state of positive energy balance. Excessive body fat mass favors high levels of insulin and insulin resistance, which promote cell growth and inhibit apoptosis, these being major risk factors of colorectal carcinogenesis (Tsugane & Inoue, 2010). Sustained physical activity can reduce body fat mass and therefore insulin levels and insulin resistance (Schoenberg, 2016; Friedenreich et al., 2017). Obese patients develop a chronic condition characterized by low-grade inflammation which promotes carcinogenesis through biologic activity of pro-inflammatory mediators such as cyclooxygenase-2 (COX-2) and prostaglandin E2 (PGE2) (Schoenberg, 2016; Pohl et al., 2018; Shawki et al., 2018). In animal studies, exercise training had impressive anti-proliferative and anti-inflammatory effects in the colon mucosa, suggesting that this mechanism may be a valid explanation of how physical activity prevents colorectal cancer (Demarzo et al., 2008). Furthermore, a group of researchers analyzed COX-2 and PGE2 status in 605 human colorectal cancer tissue samples using the molecular database from two prospective cohort studies and showed that post-diagnosis physical activity was associated with better survival only among COX-2 positive patients (Yamauchi et al., 2013). Although physical activity is beneficial for both the prevention and the improvement of prognosis, their findings support the new approach of personalized lifestyle recommendations after a diagnosis of CRC.

Another physiological pathway illustrating the beneficial effects of physical activity is related to

exercise-responsive gene expression. Enhanced nutrient metabolism in skeletal muscle influences key proteins and metabolic enzymes which are responsible for the activation and/or the inhibition of different signaling pathways that regulate transcription and translation (Booth et al., 2002; Hughes et al., 2017). A gene expression study reported low levels of vascular endothelial growth factor, angiopoietin-2 and calcium-independent phospholipase A2 in the colon of exercising rats, suggesting that physical activity can influence markers of metastasis (Buehlmeyer et al., 2008). However, few studies assessed the interaction between physical activity and gene expression in CRC among humans. One example is illustrated by a recent Korean case-control study which identified a correlation between regular physical activity, CRC risk and PITX1 polymorphism. The authors showed that subjects with the PITX1 rs647161 polymorphism are at high risk of CRC if they do not exercise regularly (Gunathilake et al., 2018).

Physical activity can modify DNA methylation patterns. In the colon of exercising rats, physical activity leads to down-regulation of the BHMT2 gene, known to be involved in aberrant methylation (Buehlmeyer et al., 2008). However, data from human studies are limited due to the inherent complexity of this type of investigations and, to our knowledge, there is no human study evaluating the effects of physical activity on DNA methylation in colon tissue. Nevertheless, in two observational studies, physical activity was correlated with enhanced methylation in peripheral blood (Luttropp et al., 2013; White et al., 2013); also, an intervention study showed that physical activity modulates DNA methylation in adipose tissue (Rönn et al., 2013). Furthermore, in an observational study, patients diagnosed with gastric adenocarcinoma practicing higher levels of physical activity presented less frequent CACNA2D3 methylation (Yuasa et al., 2009).

A growing body of evidence indicates that the enhanced levels of myokines generated in response to physical exercise can explain in part its positive effects. Myokines are proteins secreted by skeletal muscle cells, having multiple health benefits including metabolic improvement and anti-inflammatory effects in organs, in a paracrine, endocrine and autocrine manner. Aoi et al. showed that regular exercise prevents the onset of colon cancer in mouse models by inhibiting the formation of precursor lesions. Furthermore, the same authors discovered a novel myokine named secreted protein acidic and rich in cysteine (SPARC) secreted in both humans and mice that contributes to the prevention of colon tumorigenesis. Using an azoxymethane colon cancer mouse model, they demonstrated that in wild-type mice, regular low-intensity exercise reduced the formation of aberrant crypt foci and enhanced apoptosis in the colon mucosa. These antitumorigenic effects were not observed in SPARC-null mice (Aoi et al., 2013). Surprisingly, these results could not be replicated by a small clinical trial (10 participants) in humans (Songsorn et al., 2017). Other interrelated cancer-physical activity mechanisms include: DNA damage caused by oxidative stress and an impaired immune function (Friedenreich et al., 2017; Schoenberg, 2016).

Physical activity in colorectal cancer prevention

Convincing evidence shows that there is an inverse association between the risk of developing colon cancer and physical activity, whereas the relationship with rectal cancer is still elusive (3). Several studies of different designs and characterization (diverse population, BMI, various levels of physical activity, etc.) suggested that the relationship is unlikely due to confounding bias and concluded that regular physical activity is protective against both proximal and distal colon cancer.

In a meta-analysis using data prior to 2000, WHO highlighted that physical inactivity may account for 16% of the global colon cancer burden (Bull et al., 2004). Since then, a more recent meta-analysis including 52 cohort and observational studies showed that regular physical activity reduces overall risk of colon cancer by 24% in both men and women (Wolin et al., 2009). In addition, in a cohort of older adults (which due to age are at risk of developing colorectal cancer), recreational physical activity was inversely associated with the risk of colon cancer in a dose-response relationship. Some authors showed that 4-6 hours of weekly physical activity may reduce both colon and rectal cancer by 13% and 30%, respectively. Still, for colon cancer the beneficial effect was higher with increased hours of physical activity per week. Moreover, the beneficial outcome was present even if the subjects started physical activity later in life (Chao et al., 2004).

Strategies for counteracting the burden of CRC are highly desired and besides improving physical activity, other modifiable lifestyle factors can be targeted. Aleksandrova et al. (2014) developed a lifestyle index combining different factors such as: healthy weight, non-smoking, physical activity, a healthy diet and limited alcohol consumption. They demonstrated that the joint effects of multiple lifestyle factors provide better outcome in terms of prevention. Using the European Prospective Investigation into Cancer and Nutrition cohort database, they showed that participants complying with all five healthy lifestyle factors had a 37% lower risk of developing CRC compared to those with none of the healthy factors, whereas adhering to only one lifestyle factor (e.g. physical activity) decreased the risk by only 13%.

Contrary to the high amount of available data demonstrating the pivotal role of physical activity in colon cancer prevention, for rectal cancer the evidence generated conflicting results. There is a recent meta-analysis suggesting a protective effect of physical activity against rectal carcinogenesis (Moore et al., 2016). In addition, in a cohort of male workers, light and moderate/heavy occupational activity reduced the risk of rectal cancer (RR=0.71; CI: 0.36-1.37), while no association was found for leisure activity (Colbert et al., 2001). In line with the previous studies, Slattery et al. showed that vigorous physical activity was associated with a reduced risk of rectal cancer in both men (OR=0.6; 95%CI: 0.44-0.81) and women (OR=0.95; 95%CI: 0.40-0.86); also, participants engaged in vigorous activity over the past 20 years benefit from enhanced protection (Slattery et al., 2003). However, these positive results were not reported unanimously in the literature (Odegaard et al., 2013; Steindorf et al.,

2005). This controversy warrants future research and might elucidate different carcinogenic and/or protective mechanisms in the exercise-colorectal cancer interplay.

Physical activity after diagnosis of colorectal cancer

Conventional treatment of colorectal cancer includes surgery, chemotherapy and in some cases radiation. Typical side effects such as anemia, nausea, vomiting, leukopenia and diarrhea, as well as cancer-related fatigue, weakness and frequently depression, worsen the quality of life and usually impair the patients' physical capabilities, leading to increased inactivity (Schoenberg, 2016). Recommendations regarding the type of physical activity after diagnosis of cancer include aerobic, resistance and flexibility exercise for a duration that suits the unique needs of the individual. Also, patients are advised to maintain intensity and to exercise as often as able (Detroye et al., 2018). Research done so far supports physical activity during adjuvant therapy and highlights its favorable outcome in improving the quality of life, prognosis, and in counteracting the side effects of oncologic treatment.

A randomized control trial (RCT) investigated the short and long-term effect of a supervised exercise program on fatigue, physical fitness and quality of life among colorectal cancer patients (Van Vulpen et al., 2016). Patients diagnosed with colon cancer and undergoing chemotherapy were assigned to either a usual care group, being instructed to maintain their habitual physical activity pattern, or to an interventional group receiving a supervised exercise program, individualized to the patients' preferences and fitness level. Participants in the intervention group reported significantly less physical fatigue and higher physical function compared with patients in the usual care group. The authors concluded that a supervised exercise program for colon cancer patients undergoing chemotherapy is feasible, safe, may improve quality of life and has short and long-term beneficial effects.

A more recent RCT investigated the efficacy and feasibility of a 6-week home-based, unsupervised program for colorectal cancer survivors. The program aimed to increase the physical activity level to 18 MET (metabolic equivalent task) hours per week. The authors reported that 73.5% of patients in the intervention group achieved the exercise goal, while the program significantly increased physical activity levels and improved physical fitness overall (Lee et al., 2018b). In addition, Meyerhardt et al. reported that 18 MET-hours per week appears to reduce the risk of cancer recurrence and mortality in colorectal cancer patients (Meyerhardt et al., 2006b). Furthermore, an initial trial investigating the efficacy of an exercise program during neoadjuvant chemotherapy in rectal cancer patients reported no adverse events related to training. Although physical activity was well tolerated, minimal change in quality of life and cancer-related fatigue was observed (Singh et al., 2018).

Several studies investigated whether the effect of post-diagnosis physical activity is related to pre-diagnosis levels. An observational prospective study including only female patients diagnosed with stage I to III colorectal cancer reported that recreational physical activity after the cancer diagnosis may reduce cancer-specific and overall mortality. Surprisingly, patients who reported being less active before the diagnosis of cancer had better exercise-related outcomes after diagnosis, as compared to patients who used to be active before diagnosis (Meyerhardt et al., 2006a). Additionally, a more recent study evaluated the impact of recreational physical activity before and after the diagnosis of colorectal cancer on disease-specific and all-cause mortality. Pre-diagnosis physical activity levels of more than 18 MET-hours per week were associated with significantly lower colorectal-cancer specific mortality when compared with no pre-diagnosis recreational physical activity. However, the benefit in decreased mortality rates was also observed among formerly inactive patients if they reported the onset of physical activity after diagnosis (Kuiper et al., 2013).

There are studies suggesting that the beneficial effect of physical activity on prognosis is dose-dependent, even if obviously the duration of physical activities in cancer patients is limited. Previously, Meyerhardt et al. demonstrated that male patients exceeding 27 MET hours per week had a 50% better prognosis (Meyerhardt et al., 2009), while in another study, each additional post-diagnosis 10 MET hours per week (equivalent to 150 min/week of moderate physical activity) was associated with a 28% decrease in total mortality among colorectal cancer survivors (95%CI = 20-35%) (Schmid & Leitzmann, 2014). *In addition*, in a meta-analysis including 11 studies, higher levels of exercise were more beneficial *in terms of* survival compared to low levels (Wu et al., 2016).

Conclusions

1. Colorectal cancer is preventable through a healthy diet, weight control and regular physical activity.
2. Physical activity is one of the most important modifiable lifestyle factors with highly protective effects against colon carcinogenesis.
3. Physical activity during oncologic treatment can improve the quality of life, acting on both physical function and fatigue.
4. Starting physical activity after colorectal cancer diagnosis can improve prognosis and reduce mortality regardless of pre-diagnostic levels.

Conflicts of interest

There are no conflicts of interests

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