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The insulin-like growth factor axis: A biological mechanism linking physical activity to colorectal cancer survival

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ABSTRACT

Physical activity (PA) is related to colorectal cancer (CRC) mortality, with approximately 15% of CRC deaths worldwide attributable to physical inactivity. Moreover, higher levels of PA in CRC survivors have been associated with a reduced risk of the disease recurring. Despite the recognised nexus between PA and the risk of CRC, the physiological mechanisms underlying the inverse relationship between PA and mortality following CRC diagnosis are less apparent, with evidence primarily drawn from epidemiological studies. The insulin-like growth factor (IGF) axis plays a central role in cellular growth, proliferation regulation, differentiation and apoptosis. Specifically, high levels of insulin-like growth factor 1 (IGF-1) have been consistently linked to the severity of CRC tumours. Further, insulin-like growth factor binding protein 3 (IGFBP-3) regulates the bioavailability of IGF-I and therefore plays a central role in CRC prognosis. Decreasing levels of IGF-1 and increasing levels of IGFBP-3 may thus be a plausible mechanism underlying the inverse association between PA and CRC survival.

1. Introduction

Of all cancers, colorectal cancer (CRC) has the fourth highest incidence rate worldwide and it is estimated that CRC is responsible for the deaths of approximately 608,000 people each year [1]. Given these statistics, reducing CRC incidence, recurrence and improving survival have emerged as major public health priorities.

Physical activity (PA) has been specifically linked to CRC mortality, with approximately 15% of CRC deaths worldwide being attributable to physical inactivity [2] Further, epidemiological data show a significant decrease in disease-specific mortality for individuals who are physically active after diagnosis compared to those who are not [3,4]. However beyond recognising a relationship between PA and CRC survival, the biological mechanisms that underpin this association are not entirely clear. Given that the insulin-like growth factor (IGF) axis has been implicated as a key host pathway responsible for the association between PA and CRC specific mortality [5–7], using PA to influence the IGF axis may represent an effective means of reducing CRC mortality and improving survival. This paper will review the available evidence relating to PA following CRC diagnosis, the IGF axis and survival from the disease.

2. Physical activity and colorectal cancer

An inverse relationship between PA and the incidence of CRC has consistently been reported in the literature [8–10]. Furthermore, engaging in PA after CRC diagnosis is associated with 50–60% reductions in disease-specific mortality [11–14]. Despite the important role PA has for the health of survivors following CRC diagnosis, specific PA guidelines for reducing the risk of CRC-related mortality following diagnosis do not yet exist.

2.1. Physical activity and colorectal cancer incidence

Over the past ten years, three meta-analyses [8,9,15] have reported an inverse relationship between PA and the incidence of colon cancer. Samad et al. [8] analysed nineteen cohort and twenty-eight case-control studies and identified a relative risk (RR) for developing colon cancer of 0.79 when comparing the recreational PA of the most to the least active men. For women, a RR of 0.71 was identified for recreational PA when comparing the most active to least active [8]. More recently, Wolin et al. [9] found

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a RR of 0.76 for both men and women when comparing the most to the least physically-active individuals. Further, Boyle et al. [10] highlighted an inverse dose-response relationship between PA and colon cancer risk in eleven of the twenty-one studies included in their analysis.

Whilst these results offer support for the promotion of PA to reduce the risk of colon cancer, there is little evidence that PA can decrease the risk of developing rectal cancer [8,9,15]. The reason for this disparity is unknown. The closest understanding to the relationship between PA and rectal cancer is derived from studies that demarcate the colon into proximal and distal sub-sites during statistical analysis. However, findings from these studies offer no significant differences between proximal and distal colon regions with a RR of 0.73 and 0.74, respectively, when comparing the most to the least physically-active individuals [10]. A greater understanding of the physiological link between PA and colon cancer from a survival perspective may explain why rectal cancer incidence does not appear to be mediated by PA.

2.2. Physical activity and colorectal cancer survivorship

Following conventional treatment, CRC survivors who remain or become physically active have a >50% reduction in cancer-specific mortality over those who are inactive [11–13]. Indeed, researchers recommend exercise as an adjuvant to conventional treatment for those diagnosed with the disease [8,9,11–15].

Meyerhardt et al. [11] found an inverse relationship between PA and hazard ratio for CRC-specific mortality in male survivors. In a cohort of 661 men, those who engaged in more than 27 metabolic equivalent of task (MET) hours of PA per week had a CRC specific mortality hazard ratio of 0.47 compared to those who engaged in less than 3 MET-hours per week [11]. In a cohort of 573 female CRC survivors, a RR of 0.39 was found for those who engaged in at least 18 MET-hours of PA per week compared to those who engaged in less than 3 MET-hours per week [12]. Both studies found no change in statistical significance following adjustment for cancer stage (I-III), body mass index (BMI) and pre-diagnosis levels of PA. Such evidence highlights the importance of PA following diagnosis irrespective of pre-diagnosis activity levels. Although the specific frequency, intensity, type and mode of PA required for reductions in CRC specific mortality is uncertain. Meyerhardt et al. [11] have indicated that a protective effect for this measure occurs at approximately 9 MET-hours per week. This volume of PA aligns well with the current adult PA guidelines for health benefits [16].

The majority of studies that have investigated the relationship between PA and CRC survival have not reported the frequency, intensity, duration and/or mode of activity of the participants [8,9,11–15]. To a large part, this can be attributed to the limitations of self-report PA measures used in these studies, which typically estimate activity levels using MET values. It has been shown that participants tend to over-report than under-report PA when recalling previous activity levels [17]. This limits the conclusions that can be drawn from studies with respect to the 'dose' of PA required to elicit a protective effect. Research that involves structured PA interventions is required to better understand the relationships between CRC survival and PA that have been identified in prospective, case-control studies. Results from these intervention trials will help to determine the optimal 'dose' of exercise required to reduce CRC incidence and disease-specific mortality post-diagnosis. The Colon Health and Life-Long Exercise Change trial (CHALLENGE) [18] aims to address this limitation; this ongoing randomised controlled trial incorporates a multicentre PA intervention utilising instrumented measures of PA and aerobic fitness for people with stage II and III colon cancer. The primary outcome of this trial is disease-free survival, with cardiovascular fitness a secondary endpoint. This study will also track key biological markers believed to underpin the relationship between PA and colon cancer risk.

3. Insulin-like growth factors and colorectal cancer

Changes in gastrointestinal transit time, inflammation, immune function, genetic mutations, insulin and the IGF axis have all been suggested as mediators to explain the relationship between PA and CRC incidence and disease-specific mortality [19,20]. Specifically, it is believed that the IGF axis plays a central role in cellular growth, proliferation regulation, differentiation and apoptosis [21,22]. Given these mechanisms, IGFs and their binding proteins (IGFBPs) have been identified as a key research focus in CRC pathology [23].

The IGF axis has been linked to the incidence of CRC, along with the risk of tumour metastases following diagnosis [7,24]. Cross-sectional research has also found associations between the IGF axis and the graded severity of CRC carcinomas [23,25,26]. Manipulation of the IGF axis through PA may therefore be a promising therapy for preventing CRC, as well as reducing the likelihood of CRC-specific mortality post-diagnosis.

3.1. Insulin-like growth factor axis

The IGF axis consists of two polypeptide ligands (IGF-I and IGF-II), two cellular membrane receptors (IGF-IR and IGF-IIR), and six binding proteins (IGFBP-1 through IGFBP-6). IGF-I and IGF-II are produced via the endocrine, paracrine and autocrine systems [27]. Growth hormone (GH) plays a dominant role in the upregulation of IGF-I with serum levels peaking around puberty and then decreasing throughout life [28,29]. IGF-I levels are also influenced by sex and nutritional status with higher levels found in females [30], periods of excess energy intake [31] and obesity [28]. Unlike IGF-I, the release of IGF-II is GH independent and levels remain stable after puberty [27]. At a cellular level, IGF-I and IGF-II accelerate cell cycle progression through the growth phase where DNA replication occurs [32]. Analogous to this growth-facilitating effect, IGF-I and IGF-II have the capacity to block cellular apoptosis. These processes have been reported in healthy [33] and malignant tissue [34], highlighting the potential role of IGF-I and IGF-II in the progression of CRC following diagnosis.

The biological actions of IGF-I and IGF-II are mediated via two cell-surface receptors; IGF-IR and IGF-IIR [33]. Because of the structural similarities between IGF-I and IGF-II, the IGF-IR is able to bind both molecules albeit at different affinities. IGF-IR favours IGF-I, binding the molecule at a 2–15 fold higher affinity than IGF-II [35]. Unlike the IGF-IR, the IGF-IIR does not bind IGF-I; this receptor specifically binds IGF-II, and at a 500-fold affinity greater than the IGF-IR [22]. Because binding of IGF-II to the IGF-IIR results in degradation of the molecule, the intra-cellular actions of IGF-II are thought to be primarily mediated through the IGF-IR [36]. This complex association underpins the uncertainty that exists for the role of the IGF axis within the relationship between PA and CRC.

The majority (~75%) of IGF-I and IGF-II produced via the endocrine system are bound in a ternary complex with IGFBPs and an acid labile subunit (ALS) [37]. The remaining IGF-I and IGF-II circulates in free form or in a binary unit with IGFBPs only [37]. Because ALS only has an affinity for IGF-I/IGF-II that is bound in a IGFBP complex, IGFBPs are thought to control the bioavailability of IGF-I and IGF-II [38]. This is actioned via three distinct pathways; (1) transportation, (2) prolonging the half-life of IGFs and protecting them from degradation, and (3) modulating the interaction between IGFs and their receptors [39]. When combined in the ternary unit, IGF-I and IGF-II are unable to bind to the cell surface receptors, IGF-IR and IGF-IIR. This is due to the up to 50 fold higher affinity of IGFBPs for IGF-I and IGF-II over their respective receptors [39]. The outcome of this affinity is thought to be the