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Physical Activity, Dietary Fat and Colorectal Cancer

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1. Introduction

Colorectal cancer (CRC) is one of the most commonly diagnosed cancers worldwide, with over 1.2 million new cases being recorded in 2008. Global cancer statistics show that there is great (10-fold) variation in the occurrence of CRC worldwide, with the highest incidence rates in economically developed countries and regions, such as Australia, New Zealand, Europe and North America. The latest report shows that CRC incidence rates are rapidly increasing in countries within Eastern Europe and Eastern Asia, which were formerly considered low-risk areas. In some countries, e.g., the Czech Repubic and Japan, the incidence of CRC has already exceeded the peak observed in the high-risk areas. Epidemiological studies have demonstrated that the increasing incidence of CRC in these developing countries is mostly due to a higher incidence of CRC in younger age groups, which readily adopt new lifestyle habits (Jemal et al., 2011). In addition, reports have shown that persons who were born in Asia and later migrated to the United States have a higher risk of CRC than their counterparts who have remained in Asia (Flood et al., 2000).

Changes in worldwide variations in the incidence rates, together with the results of migrant studies, provide convincing evidence that the incidence rates depend largely on environmental (i.e., non-genetic) risk factors, including lifestyle. It is estimated that most cases of CRC occur sporadically (70-80%). Approximately 15% of CRC cases develop as a result of inherited factors and 5-10% of them result from known genetic syndroms, e.g., familial adenomatous polyposis (FAP) and hereditary non-polyposis colorectal carcinoma (HNPCC) (Souglakos, 2007).

There are different approaches and strategies concerning how to reduce the incidence of and mortality due to CRC. Those directed toward the treatment of CRC, i.e., surgical and therapeutic measures, are mostly costly, painful and the prognosis is not promisig. Efforts have also recently been directed toward the identification and removal of precancerous lesions (visible polypoid adenomas) through screening programs, which is a promising approach and is an important step in reducing mortality due to CRC (Orlando et al., 2008). On the other hand, efforts invested into strategies directed toward public health promotion campaigns for the prevention or reduction of risk factors in populations at high risk of CRC have been few and obviously ineffective. Recent studies have shown that there is low level of awareness of the role that physical activity plays in preventing CRC among adults in the USA and Europe (Coups et al., 2008; Keighley et al., 2004).

Epidemiological studies have shown that around 30-40% of CRC may be preventable by maintaining a healthy lifestyle and suitable diet. The available evidence suggests that the population attributable risk of physical inactivity is 13-14%, which is the same as the risk due to a Western eating pattern (Coups et al., 2008). These data, and all the aforementioned facts, show that the majority of sporadic CRC cases are preventable by adjustment of appropriate environmental and lifestyle factors (dietary habits, low body index, physical activity) and that there is a need to improve strategies of public health promotion campaigns in countries with increased risk of CRC. Public health promotion campaigns, if adopted, could have a major impact in the fight against sporadic CRC and would address many health and financial challenges.

This chapter is therefore an attempt in this direction and provides a current review of the literature on the relation between physical activity or dietary fat and CRC and the mechanisms of their interaction.

2. Physical activity and CRC

The first evidence of the preventive role of physical activity against cancer appeared in 1922, when two groups of investigators, independently of each other, observed that cancer mortality rates declined with increasing physical activity required for an occupation (Lee, 2003). In spite of these results, further investigations in this area were not undertaken until the 1980s, when investigators observed that men with sedentary jobs had a higher colon cancer risk than men with jobs requiring strenuous activity (Larsson et al., 2006). Since then, the link between physical activity and cancer risk has been examined extensively, not only for cancer of the colon and rectum but also for breast and prostate cancer and, to a lesser extent also for cancers of the endometrium, lung, ovary, testis, pancreas and kidney. Nevertheless, cancer of the large bowel is the most frequently investigated cancer in relation to physical activity in humans. There have today been over 60 epidemiological studies investigating effects of physical activity on CRC in humans. Studies have been conducted in different parts of the world (North America, Europe, Australia, New Zealand and Asia-Japan) and among different populations and races. The results of these publications are convincing and clearly indicate that physical activity protects against colon cancer in all age groups, in various racial and ethnic groups and in diverse geographic areas around the world (Friedenreich & Orenstein, 2002; Kruk & Aboul-Enein, 2006; Lee, 2003; Thune & Furberg, 2001).

2.1 Physical activity and rectal cancer
Although colon and rectal cancer share some environmental risk factors, evidence of an association between rectal cancer and physical activity is inconsistent. A meta-analysis of 19 cohort studies even estimated that physical activity provides no protection against rectal cancer (Samad et al., 2005). It is therefore currently suggested that there is no association between physical activity and rectal cancer (Friedenreich & Orenstein, 2002; Kruk & Aboul-Enein, 2006; Lee, 2003; Thune & Furberg, 2001).

2.2 Physical activity and colon cancer in humans
Summarized observational epidemiological evidence on the association between physical activity and cancer suggests that the average risk reduction for colon cancer is 30-40% (Lee,

2003) or even 40-50% (Friedenreich & Orenstein, 2002). However, estimates from meta-analyses are little lower. A meta-analysis of 19 cohort studies estimated that physical activity may reduce the risk of colon cancer on average by 20-30% (Samad et al., 2005). The World Health Organization conducted a meta-analysis using data from studies prior to 2000 and estimated that around 16% of the global colon cancer disease burden can be ascribed to physical inactivity (Bull, 2004, as cited in Wolin et al., 2009). The most reliable results are probably those from the most recent meta-analysis, which included all available case-control (24) or cohort studies (28) that had been published to June 2008, but only those that investigated the association between physical activity and colon cancer or colon and rectal cancer separately. Studies on the association between physical activity and rectal cancer or colorectal cancer combined were not included. However, this meta-analysis showed a 24% average risk reduction for colon cancer when comparing the most to the least active individuals across all studies (Wolin et al., 2009).

The results of some studies suggest that the beneficial effects of exercise may be attenuated or less consistent in women (Kruk & Aboul-Enein, 2006; Thune & Furberg, 2001). However, most studies have found no difference in colon cancer risk according to gender (Friedenreich et al., 2006), which is in agreement with the latest meta-analysis. It was estimated that the protective effect of physical activity on colon cancer is similar for men (24%) and women (21%). The risk appeared smaller in cohort studies (men=19%; women=11%) than in case-control studies (men=28%; women=32%) (Wolin et al., 2009). It has been suggested that surveys used to measure physical activity were developed mainly for men and are thus less precise in estimating household work. Women may spend between 30 minutes to 6 hours a day on household chores and family care activities and from 4 to 16 hours a day on occupational activities, which makes it challenging to assess their physical activity accurately (Howard et al., 2008).

2.2.1 Type, duration and intensity

Although it is clear that physical activity is associated with a decreased risk of developing colon cancer, details of the relationship are less clear. It is known that the frequency of muscle contraction (e.g., number of activities performed per day, week, month), duration (number of minutes or hours per day), intensity (how much energy is expended) and activity levels throughout the participant's entire lifetime, are important components of activity that can significantly affect the protective effects of physical activity on colon cancer risk (Friedenreich & Orenstein, 2002). Few studies have examined the type, intensity and duration of physical activity required. Since they used different criteria of physical activity in their tests for trends, meta-analyses of trends across these studies have not yet been conducted (Wolin et al., 2009).

Physical activity is often thought of as recreational activity or exercise but it is much more than this. Physical activity is any bodily movement produced by the skeletal muscles that results in a quantifiable expenditure of energy and thereby comprises all leisure-time activities as well as occupational activities. Leisure-time physical activity refers to sports, conditioning exercises (structured and planned activity in order to improve or maintain physical fitness), household activities, self-care activities (e.g., dressing, eating, talking, standing, walking, climbing stairs) etc. (Kruk & Aboul-Enein, 2006).

Evidence is consistent that both occupational and leisure-time physical activity can affect colon cancer risk (Wolin et al., 2009). A dose-response relationship has been noted. Higher

activity has been related to a reduced risk of colon cancer for both leisure-time and occupational physical activities (Friedenreich & Orenstein, 2002; Kruk & Aboul-Enein, 2006; Thune & Furberg, 2001; Wolin et al., 2009). Since little information is available, conclusions cannot be made about the type, intensity, frequency and duration of physical activity that is most beneficial.

Based on the current level of knowledge, it is believed that 30-60 min/day of regular physical activity of moderate to vigorous intensity is sufficient to decrease the risk of colon cancer in the general population (Friedenreich & Orenstein, 2002; Lee, 2003; Thune & Furberg, 2001).

2.2.2 Other factors

More detailed investigations on the effects of physical activity in relation to colon cancer site have recently been conducted. A few studies have evaluated the association between physical activity and colon cancer risk by anatomic site (proximal versus distal) and produced contradictory results. One study found no significant difference in risk estimates among different parts of the colon (Mai et al., 2007), while other studies found a reduction of risk only in transverse or sigmoid segments of the colon (Nilsen et al., 2008) or predominantly in the proximal colon (Lee et al., 2007).

It is believed that physical activity is associated with a reduced risk of colon cancer independently of diet or other environmental risk factors. This is supported by studies that have found that adjustment for potentially confounding factors, such as age, diet and obesity or body mass index, does not diminish the observed protective association (Friedenreich & Orenstein, 2002; Thune & Furberg, 2001).

However, it has been suggested that determination of potentially confounding variables is not always easy. When there are multiple hypothesized mechanisms, some of which may be in the causal path, the determination of confounding variables may be especially difficult. "For instance, if physical activity is associated with colon cancer through its ability to help maintain body weight, adjustment for body mass index would be inappropriate. If physical activity acts through other mechanisms, body mass index may be an important confounding variable because it is associated both with physical activity and colon cancer." An understanding of the biological mechanisms involved in the association between physical activity and colon cancer is therefore fundamental to evaluating confounding factors. In order to identify and understand the modifying effects of physical activity on other risk factors, the use of effect modification is advised (Slattery & Potter, 2002).

Slattery et al. examined confounding effect modification and observed the relative importance of high-risk diet, body mass index, energy intake and glycemic index in colon cancer prevention, which were found to be dependent on the level of physical activity (Slattery & Potter, 2002). Some studies have suggested a greater protective effect of physical activity in lean than in obese persons (Friedenreich et al., 2006; Larsson et al., 2006; Thune & Furberg, 2001). The findings of one cohort study even indicated that sedentary behavior, in particular television or video watching, is associated with an increased risk of colon cancer, independent of the time spent participating in physical activity and body mass index (Howard et al., 2008). Little is actually known about how physical activity may modify or be modified by other dietary and lifestyle factors, so conclusions based on currently available evidence can be misleading. Additional research in this direction is needed to provide public health recommendations regarding physical activity as a means of primary prevention of CRC.

2.2.3 Physical activity may affect cancer treatment and outcome

As shown above, physical activity has an important role in the prevention of colon cancer. Does physical activity also have a beneficial effect in CRC patients and survivors, though? A literature search shows that most attention on the efficacy of physical activity in colon cancer has been paid to cancer prevention. There have been few studies investigating the efficacy of activity in CRC patients. Nevertheless, available evidence suggests that physical activity may affect cancer treatment and outcome. It has been proposed that exercise during the pretreatment period may increase (boost) physical and psychological functioning, resulting in better physical preparation for treatment (shown in detail in Friedenreich & Orenstein, 2002). A study evaluating the benefits of physical activity in cancer patients and survivors shows improved functional capacity and quality of life (Johnson et al., 2009).

2.3 Physical activity and CRC in animal models

The effect of physical activity on CRC has mainly been evaluated using two rodent models of CRC, i.e., DMH/AOM animal model and Apc[Min] mice. The first model is a chemically induced animal model. Animals develop colon lesions after the application of a carcinogen (dimethylhydrazine (DMH) or azoxymethane (AOM)). Colorectal carcinogenesis in this model is a multistep process with molecular, morphological and histological features similar to those seen in human sporadic colon carcinogenesis (Perse & Cerar, 2011). The second model is a genetically predisposed model. Apc[Min] mice carry a dominant heterozygous nonsense mutation at codon 850 of the mouse homologue of the human tumor suppressor gene, APC, which results in the development of multiple adenomas throughout the intestinal tract. This mutation is implicated in both sporadic and inherited human colorectal carcinogenesis.

The first studies on carcinogen treated rats were directed at evaluating the effects of different voluntary or forced exercise (swimming, treadmill running, voluntary wheel-running) on colorectal lesions in the later stages of development (tumors, adenomas, carcinomas). These studies found that exercise significantly reduced the incidence and multiplicity of tumors, as well as the incidence and multiplicity of adenocarcinomas but had little or no effect on the incidence and multiplicity of adenomas (Basterfield et al., 2005).

Various studies have recently evaluated the effects of exercise on aberrant crypt foci (ACF), which are the first microscopically visible precursor lesions of CRC. They found that moderate-intensity exercise reduced the number of ACF in colons of DMH–treated rats (Fuku et al., 2007), low intensity exercise had no significant effect on the incidence of ACF (Lunz et al., 2008), while excessive and exhausting exercise significantly increased the number of ACF and, consequently, also the risk of development of colon cancer (Demarzo & Garcia, 2004).

In contrast to the results obtained from the chemically induced model, the results of various studies on Apc[Min] mice are inconsistent. Two studies reported that exercise (treadmill running) had no effect on the incidence of intestinal adenomas in females, while a tendency toward a reduced incidence in males was observed (Colbert et al., 2000; Colbert et al., 2003). It was then found that the beneficial effects of exercise may be related to the exercise mode (treadmill/wheel running), gender (Mehl et al., 2005) and energy balance (Colbert et al., 2006). A recent study found that voluntary wheel running exercise also inhibited tumor formation in female Apc[Min] mice (Ju et al., 2008).

The reasons for the inconsistent results are not clear. In has been suggested that different types of exercise may elicit different physiological changes related to stress hormone release

and may alter the inflammatory effects (Mehl et al., 2005). Another possible reason is the large variation in tumor yield among individual Apc[Min] mice, which may have resulted in false-negative or non-significant results when a small number of animals were used (Ju et al., 2008). Finally, it is likely that this model may be suitable for investigating and assessing the effect of physical activity on CRC development in organisms with an inherited mutation or genetic predisposition.

However, experimental studies investigating the modifying effect of other dietary and lifestyle factors in relation to the beneficial effect of exercise are scarce. One study investigated the effect of exercise in animal models maintained on different types of high-fat diet. It was found that a different type of high-fat diet (21% coconut + 2% corn oil versus 23 % corn oil) may be associated with a different outcome of colon carcinogenesis in carcinogen treated rats exposed to exercise (Thorling et al., 1994). A second study reported that 6 weeks and 9 weeks of voluntary exercise (wheel running) successfully decreased the number of intestinal polyps in Apc[Min] mice on low and high fat diets, respectively (Ju et al., 2008). We recently found that exercise has a protective role in colon carcinogenesis in carcinogen treated rats, in the case of both low and high fat consumption diets. However, in terms of the combined effect of dietary fat and exercise, our results suggest that the protective role of exercise on colon carcinogenesis may be reduced in relation to the amount and type of fat in the diet (Perse, 2010). The lack of understanding of the biological mechanisms operating between physical activity and other risk factors warrants further research.

2.4 Mechanisms of physical activity modulation

A number of plausible biological mechanisms for the protective effect of physical activity against colon cancer have been suggested. They are mostly based on various experimental results. There are currently few empirical clinical data to support any of the hypothesized biological mechanisms for the protective effect of exercise on colon cancer.

2.4.1 Effects on gastrointestinal transit time and gut microbiota

The most frequently quoted explanation for reduced colon cancer among physically active people is that physical activity accelerates the movement of stool through the colon and shortens the gastrointestinal transit time, thereby reducing the contact of potential carcinogens and cancer promoters with colon mucosa (Kruk & Aboul-Enein, 2006). Although plausible, the epidemiological evidence of an association between gastrointestinal transit time and colon cancer risk has so far been inconsistent and this explanation has not yet been directly confirmed (Friedenreich et al., 2006).

The colon contains a vast population of many types of bacteria, which have potentially important functions and may contribute to cancer development (Tammariello & Milner, 2010). It was recently found that voluntary wheel running influnced the composition of cecal microbiota, which in turn produced higher concentrations of n-butyrate. Butyrate is a short-chain fatty acid end product of bacterial fermentation in the intestines, which has been related to intestinal motility and an inhibitory effect on tumor development (Matsumoto et al., 2008).

2.4.2 Effects on blood insulin, IGF-1 and body weight

Similarities in geographic patterns and dietary and lifestyle risk factors for CRC and type 2 diabetes have led to the suggestion that there is an association between the two diseases

(Giovannucci, 2001). Based on meta-analysis of case-control and cohort studies, individuals with diabetes have an approximately 30% increased relative risk of developing CRC compared to non-diabetic individuals, regardless of gender or the anatomical site of CRC (Larsson et al., 2005). Preliminary results have shown that CRC is more common in people with increased circulating levels of insulin and glucose. A long-term increase in circulating levels of insulin may influence every step of colon carcinogenesis by stimulating cell proliferation or inhibiting apoptosis (Pisani, 2008). In addition to type 2 diabetes, obesity may cause problems with insulin metabolism and an alteration in blood glucose (explained in Murthy et al., 2009).

Physical activity can contribute to increased insulin sensitivity in skeletal muscles, both directly and indirectly through its influence on body weight (Giovannucci, 2001). Regular physical activity significantly lowers insulin levels by stimulation of the signaling pathways that contribute to increased expression and translocation of GLUT 4, which is responsible for basal and insulin-stimulated glucose uptake into the cells (explained in detail in Kramer & Goodyear, 2007).

An increasing body of evidence suggests that variations not only in the levels of insulin but also in the levels of insulin-like growth factors (IGF) may account for colon cancer and for its high incidence in Western countries. The IGF family of proteins (peptide ligands, receptors, binding proteins and proteases) are involved in the regulation of somatic growth, cell proliferation, transformation and apoptosis. Among them, IGF-1 and IGFBP-3 have been most frequently investigated in relation to CRC. It has been hypothesized that IGF-1 is implicated in the etiology of CRC as a potent mediator of cell survival and growth (for more detail see Sandhu et al., 2002). In spite of this, current evidence does not support an association between the blood level of IGF-1 and CRC. Among exercise studies in humans, 50% have found no change in IGF-1, 37% an increase in IGF-1 and 13% a decrease in IGF-1 (Friedenreich & Orenstein, 2004). Likewise, no significant association between circulating levels of IGF-1 and exercise in animal models of CRC has been found (Colbert et al., 2000; Colbert et al., 2003; Colbert et al., 2006; Ju et al., 2008; Mehl et al., 2005).

2.4.3 Effects on inflammatory modulators

A number of studies have demonstrated that regular exercise has anti-inflammatory effects, which may play a significant role in the prevention of colon carcinogenesis, as well as many other diseases, such as atherosclerosis, type 2 diabetes and breast cancer. A marked increase in circulating levels of interleukin (IL)-6 after exercise, without any muscle damage, has been observed. It was found that the level of circulating IL-6 increases in an exponential fashion (up to 100-fold) in response to exercise and declines after exercise. It has been demonstrated that plasma IL-6 increase is related to exercise intensity, duration, the mass of muscle recruited and one's endurance capacity. Recent data demonstrate that IL-6 released from contracting human skeletal muscle has anti-inflammatory, immunosuppressive, metabolic and hypertrophic effects in humans (Petersen & Pedersen, 2005; Petersen & Pedersen, 2006).

Until recently, IL-6 was generally considered to be a pro-inflammatory cytokine released primarily from immune cells. However, dramatic increases in circulating IL-6 during exercise have led to the finding that skeletal muscles are a primary source of IL-6. Skeletal muscle has thus been found to be an immunogenic and an endocrine organ, which by contraction stimulates the production and release of cytokines, which can influence

metabolism and modify cytokine production in tissues and organs (Mathur & Pedersen, 2008).

It has been found that IL-6 induces the production of cytokine inhibitors, such as IL-1 receptor antagonist (IL-1ra) and IL-10, which are anti-inflammatory molecules. IL-1ra inhibits signaling transduction through the IL-1 receptor complex, while IL-10 inhibits the production of cytokines (IL-1α, IL-1β, TNF-α) and chemokines (IL-8, protein α), which play a critical role in the activation of granulocytes, monocytes, natural killer cells and T and B cells and in their recruitment to sites of inflammation (Petersen & Pedersen, 2005; Petersen & Pedersen, 2006).

IL-6 may increase basal and insulin-stimulated glucose uptake via increased GLUT 4 translocation. IL-6 has been shown to enhance AMP-activated protein kinase (AMPK) in both skeletal muscle and adipose tissue, which stimulates fatty acid oxidation and increases glucose uptake (Nielsen & Pedersen, 2008). TNF-α has been implicated in the pathogenesis of insulin resistance related to obesity (Steinberg, 2007). Evidence exists that TNF-α blocks AMPK signaling. However, exercise may also suppress TNF-α production via IL-6 independent pathways (Petersen & Pedersen, 2006).

2.4.4 Effects on immune function

It has been suggested that the immune system plays a role in reducing cancer risk by recognition and elimination of abnormal cells through immune components. Increased inflammation and/or depressed immune function are important risk factors that may lead to several cancers, including CRC. This is in accordance with the finding of an increased incidence of cancers among patients with inflammatory bowel disease (IBD) or AIDS. AIDS patients show an increased risk not only of AIDS-related malignancies (e.g., Kaposi's sarcoma) but also other cancers, such as lung and colon. An intact immune system is usually able to destroy cancer cells as soon as they appear.

It has been demonstrated that lifestyle factors can significantly affect immune function. Regular physical activity can enhance both the functionality and number of innate immune cell components, such as cytotoxic T lymphocytes, natural killer cells, lymphokine-activated killer cells and macrophages. Moderate physical activity results in enhanced immune function, whereas exhausting exercise, overtraining or high-intensity exercise may lead to suppression of the immune function (Pedersen & Hoffman-Goetz, 2000).

2.4.5 Effects on arachidonic acid metabolism

There have been studies suggesting that exercise affects enzymes that are implicated in arachidonic acid metabolism. Arachidonic acid is part of the phospholipids in the membranes of cells and in its free form serves as a precursor in the production of eicosanoids. After liberation (by the enzyme phospholipase A2 (PLA_2)), arachidonic acid is available as a substrate for cyclooxygenases (COX) and lipoxygenases (LOX) to form prostaglandins (PG) and leukotriens (LT). Increased levels of COX-2 and PGE_2 have been found to promote the development of CRC by increasing proliferation and decreasing colonic motility and apoptosis and have been associated with aggressive tumor progression. A relationship between PG and CRC is also supported by studies showing a reduced risk of CRC with aspirin and other non-steroidal anti-inflammatory drugs (NSAID), which inhibit COX-2, thereby inhibiting PG production (Jones et al., 2003).

It has been reported that physical exercise decreased COX-2 expression in the colon mucosa of healthy untreated rats (Buehlmeyer et al., 2007) and DMH-treated rats (Demarzo et al., 2008). Exercise was found to inhibit one of the products of COX activities, PGE_2, in intestinal tumors and serum of Apc^{Min} mice (Ju et al., 2008). In rat colon mucosa, exercise was found to reduce the expression of $iPLA_2$, which is one of the PLA_2 implicated in arachidonic acid release (Buehlmeyer et al., 2008). Exercise has also been found to reduce PGE_2 levels in rectal tissue among individuals with higher levels of self-reported exercise. On the other hand, in another study, exercise had no significant effect on PGE_2 levels in colon mucosa (Abrahamson et al., 2007).

The body of evidence is currently too limited to reach any final conclusions.

2.4.6 Effects on apoptosis, proliferation, gene expression

An alteration in the control of cellular proliferation and survival may be an important step in the development of colonic neoplasms. New cells are produced rapidly and continuously from stem cells at the base of the colonic crypt. Older cells undergo apoptosis (programmed cell death) and are sloughed into the colonic lumen. To maintain crypt organization and structure, cellular proliferation and apoptosis must be tightly controlled. Failure of these controls may lead to the formation of colonic neoplasms. It has been hypothesized that exercise-induced colon cancer risk reduction might be through alterations to colon crypt cell architecture and proliferation. It has been reported that a 12-month moderate-to-vigorous intensity exercise program (60 minutes per day, 6 days per week) increased colon crypt height and decreased proliferation in men (McTiernan et al., 2006) and changed the expression of Bcl-2 and Bax protein in colonic crypts (Campbell et al., 2007).

2.4.7 Effects on oxidative status

There is growing support for the concept that reactive oxygen species (ROS), which are already implicated in a range of diseases, may be important progenitors in the pathogenesis of colon cancer. Namely, an excess of intracellular ROS results in an environment that modulates gene expression, damages cellular molecules, including DNA, which ultimately leads to mutations. In order to counteract these deleterious actions of increased levels of ROS, cells possess an antioxidant defence system, which plays a central role in protecting cells from oxidative injury. It is belived that exercise may help to prevent colon cancer due to an improvement in the cell's antioxidant defence system. It has already been demonstrated that exercise improves the antioxidant defence system in various tissues. Exercise stimulates various signaling pathways in cells, such as MAPK and NFκB, which results in increased expression of important enzymes associated with cell defence (MnSOD and GPx) and adaptation to exercise (eNOS and iNOS). Many of the biological effects of antioxidants appear to be related to their ability not only to scavenge deleterious free radicals but also to modulate cell-signalling pathways. The modulation of signalling pathways by antioxidants could thus help to prevent cancer by preserving normal cell cycle regulation, inhibiting proliferation and inducing apoptosis, inhibiting tumor invasion and angiogenesis, suppressing inflammation and stimulating detoxification enzyme activity (Kramer & Goodyear, 2007; Scheele et al., 2009; Valko et al., 2007). Exercise has been found to decrease the expression of inducible nitric oxide synthase (iNOS), as well as TNF-α, in the colon of AOM-treated mice (Aoi et al., 2010).

3. Dietary fat and CRC

In contrast to physical activity, the association between fat intake and CRC is less conclusive. In the past, dietary fat has received considerable attention as a possible risk factor in the etiology of CRC but subsequent analysis of case control studies has indicated that the positive association was at least in part due to increased energy intake (Johnson & Lund, 2007).

While epidemiological studies have produced contradictory results (Johnson & Lund, 2007), experimental studies under isocaloric conditions have provided unequivocal evidence that a diet high in saturated fatty acids (SFA), such as lard or beef tallow, and n-6 polyunsaturated fatty acid (PUFA), such as corn or sunflower oil, increases the risk of developing CRC (Dai et al., 2002; Reddy, 2000). It was recently shown that long-term consumption of a high-fat, low-calcium and vitamin D diet induces colon neoplasia in mice, without any other treatment (Erdelyi et al., 2009). Interestingly, a recent expert review on nutrition and cancer published by the World Cancer Research Fund (American Institute for Cancer Research, 2007) found suggestive evidence that food rich in animal fat (rich in SFA) is associated with an increased risk of CRC. This means that epidemiological studies are mainly supportive but are limited in quantity, quality or consistency.

In contrast, diets high in olive oil or n-9 monounsaturated fatty acid (MUFA) have shown a protective or no effect on colon carcinogenesis in animal models, while diets with fish oil or n-3 PUFA have been shown to reduce colon tumorigenesis in both initiation and post-initiation phases (reviewed in Perše, 2010). Epidemiological reports investigating the effect of n-3 PUFA on CRC are scarce. However, some studies have shown that an n-3 PUFA-rich diet suppressed the risk of colon cancer in humans. The preventive or inhibitory effect of n-3 PUFA on experimental colon carcinogenesis has been widely evaluated (Biondo et al., 2008). All these results suggest that the composition of ingested dietary fatty acids is a more critical risk factor than the total amount of fat. This is further supported by their different mode of action, which is described in the following section.

However, at the same time, it is worth emphasizing that studies on animal models have shown that the promoting effects of SFA and n-6 PUFA on CRC can be modified by various dietary factors. A relatively small fraction of n-3 PUFA (25%) in total dietary fat or supplemental calcium or antioxidants, such as vitamin D (Pence & Buddingh, 1988), vitamin A (Delage et al., 2004), as well as green tea, vitamin B6 (Ju et al., 2003) and poliphenolic extract of red wine (Femia et al., 2005), have shown an appreciable beneficial effect in lowering the risk of CRC in animal models on a high fat diet. The influence of different amounts of calcium, antioxidants and other beneficial compounds in combination with dietary lipids may therefore be complex and difficult to elucidate, particularly in epidemiological investigations. Because many dietary, as well as environmental or lifestyle factors such as physical activity, can modify the promoting effects of dietary fat on CRC, results obtained from animal models under standardized conditions may represent an important contribution to understanding the mechanisms of dietary fat involvement in colorectal carcinogenesis (Hoffman-Goetz, 2003).

3.1 Mechanisms of dietary fat modulation

Dietary fats are an important energy reserve in an organism. However, this is not their only function. Linoleic acid (n-6 PUFA) and linolenic acid (n-3 PUFA) are considered essential, since they can not be synthesized by mammals and must therefore be obtained from diet.

Lipids and fatty acids obtained from dietary fats are metabolized and incorporated into the phospholipids of the cell membranes of many cell types and serve as precursors for many biologically active molecules, as well as being important for cell signaling (Jones et al., 2003). It is generally accepted that the balance of n-6 to n-3 PUFA in the diet is of importance to human health and disease, including CRC. An alteration in fatty acid composition in the cell as a result of altered dietary fat consumption may lead to changes in all these functions, which are briefly outlined below.

3.1.1 Effects on the concentration of secondary bile acids

Experimental and epidemiological studies have shown that diets high in beef tallow, lard or corn oil increase the concentration of colonic luminal (fecal) secondary bile acids, i.e. deoxycholic acid (DOC) and lithocholic acid, whereas high dietary fish oil has no such enhancing effect. It has been found and confirmed that these secondary bile acids induce cell proliferation and act as promoters in colon carcinogenesis. Recent experiments have provided new insight into their effects on colonic epithelial cells. The results indicate that secondary bile acid DOC may act as a carcinogen, not merely a promoter (explained in detail in Bernstein et al., 2011).

3.1.2 Effects on energy balance

Energy balance has become an important concept in exploring the etiology of a number of chronic diseases, including cancer, because of its close association with weight gain and overweight - conditions known to increase the risk of many chronic diseases.

The amount of energy that is required depends in part on the composition of the food. In this regard, it is worth noting that dietary fats are more readily converted to body fat and require less energy for transformation than carbohydrates. A high fat diet therefore contributes indirectly to CRC due to increased body mass index.

3.1.3 Effects on immune function

One of the most thoroughly evaluated associations between nutrition and the immune system is that related to dietary fat. Although total fat intake has been found to increase the risk of various types of cancer, it is the type of fat that has a more important effect on the immune response and, consequently, on cancer development. PUFA have been shown to modulate cytokine production, lymphocyte proliferation, expression of surface molecules, phagocytosis, apoptosis and natural killer cell activity (the last two are closely related to cancer development). An increase in n-3 PUFA helps control the production of pro-inflammatory eicosanoids, as well as cytokine production (Valdes-Ramos & Benitez-Arciniega, 2007).

3.1.4 Effects on arachidonic acid metabolism

It has been suggested that dietary n-3 PUFA has an anti-carcinogenic role in reduction of n-6 PUFA-derived eicosanoid biosynthesis and direct inhibition of COX-2.

Dietary n-6 PUFA incorporates into the membrane phospholipids as arachidonic acid (AA), while dietary n-3 PUFA does so as eicosapentaenoic acid (EPA). AA and EPA compete for prostaglandin and leukotriene synthesis. Pro-inflammatory eicosanoids of AA metabolism are released from membrane phospholipids in response to inflammatory activation. EPA is released to compete with AA for enzymatic metabolism, inducing the production of less

inflammatory and chemotactic derivatives. Eicosanoids produced from EPA are much less potent (up to 100-fold) than the analogues produced from AA and even have anti-thrombotic and anti-inflammatory properties. The relative amounts of n-6 and n-3 PUFA provided by the diet, and so present in blood and tissues, may thus be of importance in the development of inflammatory diseases and cancers. The production of inflammatory eicosanoids is increased in response to many inflammatory stimuli (Simopoulos, 2002a). When the production of these substances is excessive, it may lead to chronic inflammation and an increased risk of cancer, since inflammation has been linked to the promotion phase of carcinogenesis (Federico et al., 2007). The increased n-6/n-3 ratio in Western diets probably contributes to reduced levels of EPA in phospholipids and, consequently, to an increased incidence of cardiovascular disease and inflammatory disorders (Simopoulos, 2002b).

Another indication of the importance of diet and n-6 PUFA in the induction and progression of CRC may be the upregulation in fatty acid binding protein (FABP)-5 during tumorigenesis, with concomitant inhibition of $\Delta 6$ desaturase activity, which are important steps in the production of AA (explained in Jones et al., 2003). Most AA in the human body derives from dietary linoleic acid (essential n-6 PUFA), which comes from vegetable oils and animal fats.

Animal studies have demonstrated that a high fat diet significantly increases the expression of PLA_2, COX-2 and PGE_2 in colon mucosa and tumors of carcinogen treated rats (Rao et al., 1996; Rao et al., 2001).

3.1.5 Effects on cell proliferation and apoptosis

The expression of Polo-like kinase-3 (PLK-3) results in cell cycle arrest or induces apoptosis. It is significantly suppressed in tumor tissue of the colon but has been found to be unchanged in colon mucosa isolated from rats on different diets. Suppression of PLK-3 was lower in tumors from rats fed n-3 PUFA than those fed n-6 PUFA (Dai et al., 2002).

Dietary corn oil and beef tallow increased BrdU incorporation and decreased apoptosis of the colon mucosa. Long-term (44 wks) high intake of corn oil and beef tallow enhanced cell proliferation through Wnt signaling and modulated the distribution of proliferating cells (Fujise et al., 2007).

High corn oil consumption decreased apoptosis and increased cell proliferation in colon of AOM treated rats (Wu et al., 2004). On the other hand, studies have indicated that n-3 PUFA has an inhibitory effect at least in part due to increased apoptosis in colonic mucosa (Hong et al., 2000; Wu et al., 2004).

3.1.6 Effects on cell signaling pathways

Studies have suggested that different types of fat may be implicated in different cell signaling pathways, rather than at the level of mutations. n-3 PUFA may interfere with Ras activation by decreasing its membrane localization and may thereby potentiate the effects of anti-Ras therapies. EPA and/or docosahexaenoic acid (DHA; another n-3 PUFA) have also been reported to prevent Akt phosphorylation or activation. n-3 PUFA incorporation into rafts or caveolae may alter the distribution or function of raft-associated signaling proteins – reduced epithelial growth factor receptor (EGFR) levels in the rafts, decreased levels of H-ras and eNOS in colonic caveolae. Alterations in raft lipid composition by PUFA have also been shown to displace signaling proteins from rafts in immune cells. n-3 PUFA decreases NFκB activity or expression in cancer cells, as well as monocytes, macrophages and T cells (Biondo et al., 2008). Peroxisome proliferators and retinoic acid–activated receptors (PPAR

and RAR, RXR) are key transcription factors regulating gene expression in response to nutrient-activated signals. A high-fat diet containing various sources of fat, such as commonly consumed in Western countries (the majority SFA), induced PPARγ and RARβ expression, concomitant with an increase in levels of COX-2 and β-catenin in colon mucosa of DMH treated rats (Delage et al., 2004). Various fatty acids have different effects on the Wnt signaling pathway (Kim & Milner, 2007). Long-term (44 wks) high intake of corn oil and beef tallow enhanced Wnt signaling. Dietary corn oil and beef tallow increased the expression of cytosolic β-catenin and cyclin D1. Expressions of Wnt2 and Wnt3 in rats fed with beef tallow and Wnt5a in rats fed with corn oil increased, with or without AOM-treatment (Fujise et al., 2007).

3.1.7 Effects on oxidative status

It has been demonstrated that dietary fatty acids affect the lipid content of tissue and the lipid peroxidation process, due to the ratio of polyunsaturated versus saturated fatty acid. A substantial increase in the PUFA content may overcome the protective action of the antioxidant system and increase susceptibility to lipid peroxidation (Avula & Fernandes, 1999). We have recently demonstrated that long-term consumption of an high-fat mixed-lipid (HFML) diet together with physical inactivity significantly increased the production of lipid peroxides in the skeletal muscle (Perse et al., 2009), suggesting that an HFML diet is an important contributor to the development of chronic diseases, including CRC. There is growing support for the concept that an excess of intracellular ROS, results in an environment that modulates gene expression, damages cellular molecules, including DNA, which ultimately leads to mutations (Valko et al., 2006). On the other hand, fish oil has been found to reduce oxidative DNA damage (Bancroft et al., 2003; Wu et al., 2004).

The large intestine is constantly exposed to ROS originating from endogenous and exogenous sources, due to oxidized food debris, toxins and high levels of iron. It has been demonstrated that dietary fatty acids affect the lipid content of tissue and result in differential susceptibility to peroxidation (Kuratko & Pence, 1991; Kuratko & Becker, 1998; Kuratko & Constante, 1998; Wu et al., 2004). It was recently shown that a high-fat, low-calcium and vitamin D diet induces oxidative stress in the colon (Erdelyi et al., 2009).

3.1.8 Beneficial role of n-3 PUFA before or during chemotherapy

Based on considerable evidence showing different beneficial effects of n-3 PUFA, it has been suggested that n-3 PUFA may improve the outcome of patients undergoing abdominal cancer surgery (Valdes-Ramos & Benitez-Arciniega, 2007). Since n-3 PUFA enrichment can affect the physical properties of cell membranes, altering membrane fluidity and increasing the permeability of tumor cells, it has been proposed that n-3 PUFA consumption may modify the influx and efflux of drugs into or out of tumor cells. However, elucidation of mechanisms is essential for ensuring both the optimal efficacy of a drug and for identifying the target level at which to modify the diet or supplement with n-3 PUFA, in order to optimize the benefits to the patient (Biondo et.al, 2008).

4. Conclusion

Evidence that physical activity affects the risk of colon cancer has been provided by numerous epidemiological and experimental studies and reviewed extensively. Although strong evidence exists that regular physical activity is associated with decreased risk of

colon cancer, little is known about the type, intensity, frequency and duration of physical activity that is most benefical. Evidence is consistent that both occupational and leisure-time physical activity can affect the risk of colon cancer. Based on the current level of knowledge, it is believed that 30-60 min/day of regular moderate to vigorous intensity physical activity is sufficient to decrease the risk of colon cancer in the general population.

The relation between dietary fat and CRC is less conclusive. Experimental studies suggest that the composition of ingested dietary fatty acids is a more critical risk factor than the total amount of fat. This is further supported by their different modes of action. It has been proposed that the increased n-6/n-3 ratio in Western diets probably contributes to an increased incidence of cardiovascular disease and inflammatory disorders, as well as at least in part CRC. There is increasing body of evidence that the consumption of n-3 PUFA can impact on immune functions, as well as alter gene expression and transcription factor activity in normal and cancer cells. It has also been found to reduce CRC risk and is suggested to have a beneficial role before or during chemotherapy, and even improve drug uptake.

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6. References

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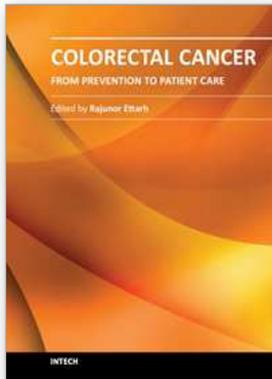
Colorectal Cancer - From Prevention to Patient Care

Edited by Dr. Rajunor Ettarh

The projections for future growth in the number of new patients with colorectal cancer in most parts of the world remain unfavorable. When we consider the substantial morbidity and mortality that accompanies the disease, the acute need for improvements and better solutions in patient care becomes evident. This volume, organized in five sections, represents a synopsis of the significant efforts from scientists, clinicians and investigators towards finding improvements in different patient care aspects including nutrition, diagnostic approaches, treatment strategies with the addition of some novel therapeutic approaches, and prevention. For scientists involved in investigations that explore fundamental cellular events in colorectal cancer, this volume provides a framework for translational integration of cell biological and clinical information. Clinicians as well as other healthcare professionals involved in patient management for colorectal cancer will find this volume useful.

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