Chapter

Effectivity and Modulating Pathways for the Prevention of Colorectal Cancer: Diet, Body Fatness, Physical Activity, and Supplementation

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Abstract

The global prevalence of colorectal cancer (CRC) is currently the highest in high-income countries. However, a rapid increase in prevalence is starting to emerge in many low-income and middle-income countries. This phenomenon is thought to be related to the adoption of a Western lifestyle, characterized by a lack of physical activity, the consumption of refined cereals, as well as highly processed foods. Other characteristics include a reduction in fruit and vegetable intake with a concomitant increase in the consumption of foods that are energy dense, but lacking in micronutrients. Coupled to the above dietary and lifestyle changes is the advent of an increased prevalence of body fatness and central obesity, as well as a dietary intake that lends itself to increasing the risk of developing CRC. As there are observed inconsistencies when appraising the effectivity of dietary and lifestyle-cancer relationships, this chapter will provide an overview of the current body of evidence regarding the role of diet and proxies for lifestyle in terms of their preventative or causative roles in the development of CRC. In addition, the strength of scientific evidence will be alluded to, as well as the modulating pathways responsible for CRC causation or protection.

Keywords: alcohol, body fatness, colorectal cancer, dairy products, diet, dietary fiber, fruits, vegetables, physical activity, processed meat, red meat, supplements

1. Introduction

Globally, colorectal cancer (CRC) is the third most commonly diagnosed malignancy and the fourth leading cause of cancer-related mortality, accounting for about 1.4 million new cases and almost 700,000 deaths in 2012 [1]. Its disease burden is expected to increase by 60%, resulting in over 2.2 million new cases and 1.1 million cancer deaths by 2030 [2]. The distribution of CRC burden varies widely across regions, as more than two-thirds of all cases and about 60% of all deaths occur in countries with a high or very high Human Development Index [1]. However, CRC is considered to be one of the strongest indicators of the global cancer transition, as countries undergoing rapid social and economic transition

are displaying rapid increases in the prevalence of cancers that are already more widespread in high-income countries [2]. Hence, CRC incidence and mortality rates are still rapidly increasing in many low-income and middle-income countries, while stabilizing or decreasing trends are being observed in highly developed countries where rates remain among the highest in the world [2]. As patterns and trends in CRC incidence and mortality are related to development levels, their incremental changes could be indicative of the adoption of a more Westernized lifestyle [2].

Targeted interventions tailored to available resources, including primary prevention, are necessary to decrease the global prevalence of CRC [2], as primary prevention dietary habits and other healthy lifestyle factors such as physical activity (PA) are viewed as the most effective and affordable strategy for curbing this global epidemic [3, 4]. In addition, genetic predisposition and environmental factors including diet and PA are considered to be the two main causes of CRC [3, 5].

Due to observed inconsistencies when appraising the effectivity of dietary and lifestyle-cancer relationships, this chapter will provide an overview of the current body of evidence regarding the role of diet, individual foods, alcoholic beverages, vitamins, body fatness, physical activity, and dietary supplements in terms of their classification as preventative or causative in the development of CRC. In addition, the strength of scientific evidence will be alluded to, as well as the modulating pathways responsible for reaping protective benefits or promoting carcinogenesis. Inconsistent findings across scientific literature related to dietary prevention of CRC include but are not limited to discrepancies in study design, dietary interventions assessed, baseline eating patterns, and populations sampled [6].

2. Diet

2.1 Dietary fiber

Dietary fiber refers to carbohydrate polymers of plant origin that may or may not be associated to plant lignin [7]. There is convincing evidence that consuming wholegrains and foods containing dietary fiber decrease the risk of developing CRC [8]. A meta-analysis of prospective studies noted a 10% reduction in CRC risk for every 10 g of total dietary fiber consumed on a daily basis [9]. An analysis of specific sources of dietary fiber found that cereal fiber was associated with a dose-dependent reduction in risk of 10% for every 10 g consumed; however, fruit fibers, vegetable fibers, and legume fibers were not associated with a significant reduction in risk. A meta-analysis of case-control studies and cohort studies on dietary fiber intake and the incidence of CRC adenoma reported similar findings [10].

The European Prospective Investigation into Cancer and Nutrition (EPIC) supports the protective effect of dietary fiber, as the consumption of cereal fiber was significantly and inversely associated with colorectal cancer, colon cancer, and rectal cancer [11]. A significant inverse association was also noted between colon cancer and combined fruit and vegetable fiber intake, although the study was limited by dietary intake assessment conducted at baseline [12].

The HELGA prospective study agrees with previous studies, as a 26% reduction in colon cancer risk in men was reported for every 10 g of dietary fiber consumed on a daily basis. However, the association was not significant in women, thereby suggesting that dietary fiber may be protective against CRC, but other factors such as phytochemicals, energy intake, body weight, and genetics may be equally influential, as is general dietary pattern [13]. This finding serves to demonstrate that consuming dietary fiber from a variety of sources (cereals, fruits, and vegetables)

protects against the development of CRC in a dose-dependent manner. Based on the convincing evidence available, it would be reasonable to recommend an increased intake of wholegrains to help reduce the risk of CRC [4].

2.1.1 Mechanism

Dietary fiber found in wholegrains may protect against the development of CRC by increasing fecal bulk through binding water and decreasing colonic transit time, thereby reducing the potential for fecal mutagens to interact with the colon mucosa, lowering the concentration of potential carcinogens, and exposing the colon mucosa to potential carcinogens for shorter period of time [4, 12, 14–17]. In addition, dietary fiber is fermented by intestinal microbiota into short-chain fatty acids (SCFAs) such as butyrate, which in experimental studies was shown to have antiproliferative and pro-apoptosis properties [4, 14–18]. SCFAs also lower fecal pH in the colon, thus providing a healthy intestinal environment [18], as well as inhibit chronic inflammation and cancer cell migration/invasion in the colon. However, these activities are only effective within certain physiological concentration ranges of SCFAs [18].

Other mechanisms include a reduction in secondary bile acid production [14], as well as enhancing the health of colonocytes [12] by modifying the composition of gut microbiota that can enhance immunity [18]. High-fiber diets may also reduce insulin resistance, a risk factor for CRC [7, 8, 14–16], by decreasing insulin growth factor (IGF)-1 activity, decreasing systemic inflammation via the production of SCFAs, and enhancing levels of colonic microbiota, thereby strengthening the intestinal barrier [4, 15, 16]. The anticarcinogenic properties of wholegrains also include being a source of antioxidants such as vitamin E, selenium, copper, zinc, and phytochemicals, as well as decreasing body adiposity [4, 14]. Wholegrains are also sources of lignans, phytoestrogens, and phenolic compounds [14], with many of these bioactive compounds being largely found in the bran and germ of the grain. To illustrate the plausible anticarcinogenic properties of several phenolic acids, experimental studies have showcased their ability to stimulate anti-oxidative activity [19].

2.2 Dairy products

Dairy products include milk (whole or skim milk), cheese (fresh, cottage, and hard cheese), and yogurt [17]. There is strong probable evidence that consuming dairy products, i.e., total dairy, milk, cheese, and dietary calcium, decreases the risk of CRC [8]. Dose-response meta-analyses of dairy products, milk, and dietary calcium were statistically significant with little or no heterogeneity. However, the evidence for cheese was not as strong as for other dairy products, with prospective studies finding no association between cheese intake and CRC risk, thus qualifying the level of evidence as not conclusive [7]. A pooled analysis reported significant inverse associations when comparing the highest with the lowest levels of milk intake and dietary calcium. Hence, there is evidence of plausible mechanisms in humans [8]. As there is probable evidence that milk consumption protects against CRC, it may be reasonable to encourage the consumption of milk for the prevention of CRC [4].

2.2.1 Mechanism

Dairy products contain a variety of bioactive compounds that could be related to simultaneous positive or negative effects on carcinogenesis. The overriding theory underpinning the possible protective effect of dairy products against cancer risk is related to their calcium and to a lesser extent, their vitamin D, lactoferrin, and fermentation products [4, 20, 21]. In addition, dairy products have the ability to

modulate inflammatory responses [22]. Lactic acid-producing bacteria may also protect against CRC [20], while the casein and lactose in milk may increase calcium bioavailability [4, 23]. Lastly, the anticarcinogenic effect of milk is also related to its conjugated linoleic acid and butyric acid content [4].

2.3 Red meat

There is strong probable evidence from epidemiologic studies that the consumption of red meat, including beef, pork, lamb, and goat from domesticated animals, increases the risk for developing CRC [7, 8]. The evidence for red meat has consistently shown a positive association in the dose-response meta-analyses for colorectal, colon, and rectal cancer. Despite the result being positive, it was not significant for colorectal and rectal cancers but significant for colon cancer. As there is evidence of plausible mechanisms operating in humans, the consumption of red meat is probably a cause of CRC [8]. In contrast to red meat, the consumption of poultry and fish has been associated with a modest reduction in CRC incidence. This is concordant with the concept that there are components other than fat and protein in red and processed meat that contribute to carcinogenic effects. Thus, based on current evidence, it would be reasonable to recommend the substitution of red and processed meat with poultry or fish, as it can serve as a strategy for CRC prevention [4].

2.3.1 Mechanism

Red meat consists of compounds such as haem iron (HI) that facilitates the endogenous formation of N-nitroso compounds (NOCs) such as nitrosylated HI, catalyzing its formation from natural precursors in the gastrointestinal tract (GI), as well as through lipid peroxidation in the GI [4, 24, 25]. In addition, HI can induce oxidative stress, colonocyte proliferation through the lipid-peroxidation pathway, and production of free radicals in the colonic stream [25]. The carcinogenic compounds forming during processing and cooking include NOCs and polycyclic aromatic hydrocarbons (PAHs) [25]. Cooking red or processed meat at high temperatures produces mutagens such as PAHs and heterocyclic aromatic amine (HAAs) [4, 25], both of which have been linked to CRC development in experimental studies [26]. The latter are genotoxic, and the extent to which HAAs' conversion to genotoxic metabolites occurs as a result of amino acids and creatinine reacting at high cooking temperatures is higher in humans than experimental animals. HAAs become DNA-alkylating agents, inducing DNA mutations after activation by various metabolizing enzymes. The GI microbiota adapts to meat intake and HAAs, resulting in HAAs possibly becoming more genotoxic in those with a high meat intake. However, the majority of studies that have investigated meat and phenotype interactions did not yield convincing evidence. It is therefore probable though that heat-induced mutagens found on the surface of well-done red meat can cause colon cancer in those with a genetic predisposition. NOCs, PAHs, and HAAs are considered to be genotoxic by acting directly on DNA, causing point mutations, deletions, and insertions. However, there is little direct evidence that these mechanisms come into play following meat consumption. A high consumption of HI (excluding other forms of iron), NOCs, HAAs, and PAHs has been associated with an increased risk of colorectal tumors, with a few exceptions. Genetic variations in NOCs' and HAAs' metabolism may alter the relationship between the consumption of red meat and the risk of developing colon cancer. However, there is substantial supporting mechanistic evidence regarding HI, NOCs, and HAAs being involved in colon carcinogenesis. A high consumption of red meat (300–420 g/day), increased levels of DNA adducts, is presumed to be derived from NOCs, in exfoliated colonocytes or rectal biopsies [25].

2.4 Processed meat

There is strong convincing evidence that consuming processed meat, i.e., meats preserved by smoking, curing, or salting, or addition of chemical preservatives, increases the risk of CRC [7, 8]. The evidence is generally consistent by showing an increased risk of CRC with increased consumption of processed meat. The dose-response meta-analysis showed a significant increased risk of CRC at consumption levels of 50 g/day [8].

2.4.1 Mechanism

The carcinogenic compounds that form during processing include NOCs and PAHs. NOCs are exogenously introduced from nitrates and nitrites added during the preservation process [25, 27] but can also be formed endogenously. In processed meat, HI is nitrosylated because curing salt contains nitrate or nitrite. There is evidence that nitrosylated HI promotes carcinogenesis at doses that are five to six times lower than non-nitrosylated HI [25].

However, it is likely that a combination of mechanisms contribute to a higher risk of developing CRC among those who consume high quantities of processed meat. Similar to red meat, processed meat is high in fat, protein, and HI, which can promote carcinogenesis through the mechanisms described under red meat [25, 26]. In addition, processed meats such as sausages are often cooked at high temperatures, leading to increased exposure to HAAs and PAHs [25, 27], with levels varying according to meat type, temperature, cooking time, and method [25]. The invariably higher fat content of processed meat when compared to red meat may stimulate carcinogenesis through synthesis of secondary bile acids. However, human data supporting this hypothesis are weak [27].

2.5 Fruits

A dose-response meta-analysis showed no significant association between fruit consumption and CRC. There was evidence of a nonlinear dose response of CRC and fruit intake showing a significant increased risk at low levels (less than 100 g per day) of intake [7, 8]. Hence there is limited suggestive evidence available that a low consumption of fruit increases the risk of colorectal [8].

2.5.1 Mechanism

Apart from fiber content, fruits are a rich source of vitamins C and E, as well as numerous bioactive compounds which may have an anticarcinogenic potential. These include folate, flavonoids, polyphenols, and limonene [4, 28]. Many of these compounds have potent anti-oxidative properties which could inhibit cellular damage and exposure to reactive oxygen species [28].

2.6 Non-starchy vegetables

Based on epidemiological studies, the term vegetables may cover different categories, namely, total vegetables (non-starchy vegetables and starchy vegetables), non-starchy vegetables, fresh vegetables (as opposed to preserved vegetables), and raw vegetables (excluding cooked vegetables) [7]. There is limited suggestive evidence that a low intake (less than 100 g per day) of cruciferous vegetables and non-starchy vegetables might increase the risk of CRC [7, 8]. However, there is also limited evidence that a high intake of fruits and vegetables protects against

CRC. Considering the well-establish cardiometabolic benefits of adequate fruit and vegetable intake, it would be reasonable to recommend increasing intake among populations with very low consumption [4].

2.6.1 Mechanism

The consumption of vegetables provides a large number of potential anticarcinogenic components that include dietary fiber, carotenoids, vitamins C and E, selenium, folate, dithiolethiones, glucosinolates and indoles, isothiocyanates, flavonoids, polyphenols, protease inhibitors, plant sterols, allium compounds, and limonene [7, 29]. It is possible that a combination of these nutrients and phytochemicals is responsible for the lower CRC risks associated with vegetable consumption [8], due to their antioxidant and antiproliferative activities, modulating xenobiotic and hormonal metabolism and immunity [30, 31]. Vegetables are an important source of micronutrients, notably folate that plays an important role in DNA synthesis and methylation and in the expression of genes involved in carcinogenesis [32]. Anticarcinogenic compounds such as folate, vitamins, fiber, minerals, flavonoids, and glucosinolates are found in cruciferous vegetables [4].

2.7 Alcoholic beverages

Alcoholic beverages contain ethanol that is formed during fermentation. In epidemiological studies, exposure to alcoholic beverages is examined by measures such as drinking or not, the number of drinks/glasses or 10 g units consumed per day or per week [7]. Concerning CRC associations, the evidence is considered to be convincing in men and probable in women [7, 33], as there is convincing evidence that the consumption of approximately two or more alcoholic drinks per day (30 g) increases the risk of CRC with a significant risk being observed for colorectal, colon, and rectal cancer [8]. An intake of 30 g per day is associated with a 16% increase in CRC risk, whereas an intake of 45 g per day increases the risk by 41% [34], suggesting a dose-response relationship in which the higher the intake, the higher the risk [33].

2.7.1 Mechanism

The mechanisms whereby chronic alcohol consumption has an effect on the development of CRC are diverse. Acetaldehyde (the first compound formed in ethanol metabolism) has mutagenic and carcinogenic activity. It is thought that it plays a critical role in CRC onset via toxic metabolites of ethanol oxidation that can be carcinogenic to colonocytes [35, 36]. Higher ethanol consumption can also induce oxidative stress through the increased production of reactive oxygen species which are genotoxic and carcinogenic [37]. Alcohol may also act as a solvent for cellular penetration of dietary or environmental (e.g., tobacco) carcinogens, affect hormone metabolism, and interfere with retinoid metabolism and with DNA repair mechanisms [38].

3. Vitamins

3.1 Vitamin C

There is limited suggestive evidence that consuming foods containing vitamin C might decrease the risk of colon cancer. However, no conclusion was drawn regarding rectal cancer [8]. Although the evidence was limited, it was generally consistent and the dose-response meta-analysis showed a significant decreased risk at a level of 40 mg per day [8].

3.1.1 Mechanism

The biological plausibility to support a protective effect of vitamin C on CRC development is related to its potency as an antioxidant, thereby reducing levels of reactive oxygen species, inhibiting lipid peroxidation, and reducing nitrates [4, 28]. Vitamin C has also been shown to inhibit carcinogen formation in experimental models and to protect DNA from mutagenic effects [39]. Other mechanisms include inhibition of cell proliferation, pro-apoptosis, and a reduction in inflammation [4].

3.2 Vitamin D

There is limited suggestive evidence that foods containing vitamin D, serum vitamin D, and supplemental vitamin D might decrease the risk of CRC [8]. For foods containing vitamin D, a dose-response meta-analysis showed a significant decreased risk for CRC. For supplemental vitamin D, the dose-response meta-analysis showed a significant decreased risk for colon cancer, whereas for plasma/serum vitamin D, the dose-response meta-analysis did not exhibit a significant association with CRC. Two published meta-analyses reported significant inverse associations. Hence, the WCRF/AICR, Continuous Update Project report, noted that plasma/serum vitamin D status can be influenced by sun exposure, obesity, seasonality, smoking, and measurement error. There is evidence of plausible mechanisms in humans [8]. Convincing data from epidemiologic and experimental studies support the potential chemopreventive effects of vitamin D against CRC development, although the evidence from randomized controlled trials (RCTs) is inconclusive [4].

3.2.1 Mechanism

Underlying mechanisms for an effect of vitamin D on CRC have been predominantly studied in vitro and experimental models. Hence, limited data is available in humans [8]. However, these studies suggest a role of circulating vitamin D through its active form, 1 α, 12-dihydroxyvitamin D3 [1,12(OH)2D3], in controlling cell growth, by reducing proliferation and by inducing differentiation and apoptosis [4, 40]. Other alleged mechanisms related to a higher vitamin D status are related to improved innate and adaptive immune function, inhibition of angiogenesis, reduced inflammation, and regulation of microRNA expression [4, 40–42], as well as inhibition of invasion and metastasis and suppression of angiogenesis [4].

4. Body fatness

Body fatness and abdominal obesity is normally estimated by body mass index (BMI), waist circumference, and waist-to-hip ratio [7]. There is strong convincing evidence that body fatness increases the risk of colorectal, colon, and rectum cancer [7]. However, cognizance should be taken of the fact that these anthropometric measurements have limitations as they do not distinguish between lean and fat mass [8]. Evidence supporting a clear dose-response association was related to showing a significant increased risk of CRC with an increased BMI [8, 43, 44]. There is evidence of a nonlinear dose response, whereby the increased risk is higher at a BMI beyond 27 kg/m^2 for CRC. Significant positive associations were observed for CRC in the dose-response analysis for waist circumference and waist-to-hip ratio [8]; hence, the level of evidence is being referred to as convincing for abdominal obesity [33]. In contrast to the vague findings regarding the role of individual nutrients or foods, the strong consistent association between obesity and CRC (at least in men)

further underscores the importance of combined integrated effects of nutrients/foods over their individual effects. These effects probably do not only reflect the imbalance between energy intake and expenditure but the often suboptimal quality of the diet associated with the development of obesity [4].

4.1 Mechanism

Overnutrition increases the supply of glucose and fat that can feed into metabolic reprogramming to fuel cancer cell proliferation. In addition, glycolysis has been shown to be enhanced in cancer cells of obese individuals. As obesity is often associated with metabolic syndrome (MS) and diabetes, characterized by hyperglycemia and/or hypertriglyceridemia, an abundance of circulating nutrients are available for tumor development, even between feeding periods [45]. Autophagy, the process whereby cancer cells digest and recycle their cellular contents during periods of low nutrient availability, can provide cancer cells with lipids, amino acids, and nucleotides required for proliferation [46]. Obesity has been shown to induce autophagy, particularly in adipocytes [45]. These obesity-associated metabolic adaptations facilitate the development of cancer traits that include insensitivity to anti-growth signals, resistance to cell death, and deregulation of cellular energetics [47]. Hence, interactions between cancer cell energetics and systemic metabolism highlight unique therapeutic strategies and interventions, particularly among obese individuals, as cancer cells may be more sensitive to metabolic interference, having already committed to metabolic reprogramming [45].

In addition, obesity and MS are associated with abnormalities in insulin signaling, growth factor signaling, and glucose metabolism [48]. One growth factor implicated in cancer risk and progression is insulin-like growth factor (IGF)-1. Hyperglycemia and hyperinsulinemia, diagnostic criteria of MS, increase IGF-1 production and bioavailability. Furthermore, hyperglycemia suppresses IGF-1-binding protein synthesis, while hyperinsulinemia promotes expression of growth hormone receptor and subsequent IGF-1 synthesis [48]. Growth and survival functions of IGF-1 give it the potential to have an impact on many characteristics of cancer, including sustained proliferative signaling, insensitivity to anti-growth signals, induction of angiogenesis, and metastatic potential [49]. As a result, elevated IGF-1 has been established as a risk factor for CRC [45].

Higher body fatness is associated with increased insulin levels, which can promote cell growth and inhibit apoptosis and has been linked to a greater risk of CRC in humans [50, 51] and in experimental studies [52]. Body fatness also stimulates the body's inflammatory response, which can promote CRC development [53, 54]. Overall, there are convincing mechanistic data supporting a link between body fatness and CRC [8].

5. Physical activity

Physical activity (PA) includes all movements performed in daily life, including sport, whether recreational or competitive [30], as well as that performed in occupational, transport, recreational, and household settings [7]. In epidemiological studies, PA is computed by combining intensity, duration, and frequency of different types of PA, with subjects being classified into three levels of PA, namely, low, moderate, or high. PA is usually divided into four types of activity related to occupational, transport, recreational, and household settings. Total PA is calculated as the sum of the four types or any of the four types that are presented as all-type PA. Thus a major barrier to conducting meta-analyses is the disparity between the measures of PA [7].

There is convincing evidence that all types of PA, when comparing the highest and lowest levels, are protective against colon cancer with a significant inverse association being observed for total PA and CRC. However, no significant associations were observed for rectal cancer and either total or recreational PA when comparing the highest and lowest levels. For recreational PA and colon cancer risk, three published meta-analysis reported inverse associations. In addition, there is robust evidence for mechanisms operating in humans. However, dose-response relationships could not be determined [7, 8]. The protective effect was similar for proximal and distal colon cancer and was stronger for men than women [7]. More physically active subjects had a 24% decreased risk of CRC compared to those who lead a more sedentary lifestyle [55]. It has been reported that those who exercise regularly decrease their CRC risk by 40%, regardless of BMI [56]. In addition, 30 min of daily moderate exercise result in an 11% reduction in CRC [57].

5.1 Mechanism

PA reduces body fatness and therefore has a beneficial effect on CRC risk, possibly due to a reduction in insulin resistance and inflammation [50, 53, 54]. However, it is unclear whether PA that is not accompanied by weight loss has a significant impact on these pathways. Other mechanisms through which PA may lower CRC risk include the stimulation of digestion and reduction of gastrointestinal (GI) transit time, although robust data to support this mechanism in humans is limited [58]. Overall, mechanistic data to support a link between PA and CRC are moderate in strength [8].

6. Supplementation

6.1 Calcium changes made to this section are indicated in blue

The Women's Health Initiative failed to show a significant relationship between calcium supplementation and the risk of developing CRC among postmenopausal women [59], while a meta-analysis of cohort studies reported a significant inverse relationship for colon and CRC when comparing the highest to lowest levels of calcium supplementation [60]. As there is evidence of plausible mechanisms in humans, the Continuous Update Project (CUP) panel concluded that taking calcium supplements probably protect against CRC, based on evidence derived from a dosage of more than 200 mg per day [8]. The evidence was generally consistent and showed inverse associations across a range of intakes (200–1000 mg). RCTs reported a nonsignificant inverse association for calcium and vitamin D supplementation compared to placebo, after excluding women using calcium or vitamin D supplements at baseline. Although no dose-response meta-analysis could be conducted, six of the eight cohort studies reported inverse associations [8]. Predominant evidence indicates an increased CRC risk among individuals with a calcium intake lower than 700–1000 mg/day. It would therefore be reasonable to encourage individuals to increase their calcium intake to a level above this range, while recognizing that available data yielded inconsistent results [4].

6.1.1 Mechanism

A proposed mechanism for the protective properties of calcium against CRC is its ability to bind to unconjugated bile acids and free fatty acids (FFAs), thereby limiting their toxic effects on the colorectum [4, 61]. Cell culture studies suggest that it may also suppress cell proliferation and promote cell differentiation and

apoptosis, likely by influencing different cell-signaling pathways [4, 62]. Calcium may also prevent colonic K-ras mutations and inhibit haem-induced promotion of colon carcinogenesis [63, 64]. In addition, calcium also inhibits oxidative DNA damage and modulates CRC-related cell-signaling pathways [4].

6.2 Multivitamins-multivitamins were kept under the heading of "Supplementation" as the content under "Vitamins" in Section 3 is related to vitamins derived from whole foods and not supplements

There is evidence that consuming multivitamin supplements might decrease the risk of CRC cancer [8]. However, the evidence is limited but generally consistent [8]. One RCT in men reported a nonsignificant inverse association for multivitamin supplementation compared to placebo. The analysis of highest versus lowest users of supplements showed a significant decreased risk of CRC. One published meta-analysis on CRC and colon cancer reported significant inverse associations. There is evidence of plausible mechanisms in humans [8].

6.2.1 Mechanism

Multivitamin supplements consist of a combination of several, or in some instances, many vitamins, thereby making it challenging to determine what exactly the active ingredient is. Numerous vitamins included in multivitamin supplements have been shown to neutralize free radicals and reactive oxygen species and to prevent lipid peroxidation [65].

7. Conclusion

Based on the dietary- and lifestyle-related evidence presented, there is convincing evidence that PA decreases the risk of developing CRC, while the consumption of processed meat increases risk. In addition, the consumption of alcoholic beverages is a convincing cause of CRC, as is higher body fatness. Probable evidence regarding a decreased risk for the development of CRC is available for the consumption of wholegrains, foods containing dietary fiber, dairy products, and calcium supplements. There is also probable evidence that the consumption of red meat probably causes CRC. Limited suggestive evidence regarding the prevention of CRC exists for foods containing vitamin C and vitamin D and taking a multivitamin supplement, while the same level of evidence for increasing CRC risk is related to a low consumption of non-starchy vegetables and fruits.

For the prevention of cancer, it is recommended that the general population should strive toward maintaining a healthy weight, being physically active, eating a variety of foods, and limiting alcohol intake. However, recommendations aimed at the prevention of CRC, include keeping body weight within a healthy range, being physically active, making wholegrains, vegetables, fruit, and legumes a major part of the usual diet, and limiting the consumption of fast foods and other processed foods high in fat, starches, and sugars. Furthermore, red meat should be consumed in moderate amounts, while little if any processed meat should be consumed. It is best not to drink alcohol and not using supplements for the prevention of CRC.

Conflict of interest

The author has no conflict of interest associated with this publication.

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