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The Role of Diet and Lifestyle in Colorectal Cancer Incidence and Survival

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Abstract: Colorectal cancer is one of the most prevalent malignancies in the population, resulting in significant morbidity and mortality world-wide. Identifying modifiable risk factors to reduce the incidence and morbidity of colorectal cancer is beneficial on an individual and public health level. Protective lifestyle factors against colorectal cancer incidence includes high levels of physical activity, healthy diets rich in fruits and vegetables, fish, dietary fiber, dairy, and all essential vitamins and minerals. Risk factors for increased colorectal cancer incidence includes a diet high in red and processed meat, alcohol, and tobacco. The evidence regarding the influence of specific vitamins and minerals is still evolving, as well as the etiology behind their mechanism of action in colorectal pathogenesis. Ongoing epidemiological studies are underway to determine the effects of

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various lifestyle factors on colorectal cancer survival. Overall, lifestyle modification is essential for prevention and treatment of colorectal cancer for improved patient outcomes.

Keywords: colorectal cancer incidence; diet and colorectal cancer; lifestyle and colorectal cancer; red meat and colorectal cancer; survival in colorectal cancer

INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer world-wide and the second-leading cause of overall cancer deaths (1). These cancers develop most commonly from polyps within the colon or rectum that undergo a dysplastic process to progress to adenocarcinomas through the adenoma-carcinoma sequence (2). Although there are many genetic syndromes associated with familial CRC, the vast majority of CRC, approximately 70%, occur sporadically. The development of these non-hereditary tumors is influenced by a variety of environmental factors. As CRC is a common and morbid disease, there has been extensive epidemiological investigation to identify the modifiable risk factors associated with both the incidence of CRC and factors influencing cancer survival. Through a comprehensive review of current literature, this chapter outlines how physical activity, diet, vitamin and minerals, and other lifestyle factors influence the incidence and survival of CRC.

PHYSICAL ACTIVITY

The benefit of daily physical activity of moderate intensity for 30 minutes or more is well established in improvement of overall health. There have been many observational studies that have demonstrated the protective effects of high levels of daily physical activity in the prevention of CRC. There is strong evidence to support an approximate 20% relative risk reduction of developing CRC with high levels of recreational physical activity, in a dose-response relationship (3, 4). A 42% improvement in both all-cause and colon-cancer specific mortality in CRC patients with high levels of physical activity after cancer diagnosis has also been demonstrated (3).

On the other side of the same coin, there has been increasing evidence to suggest that individuals who live a sedentary lifestyle, meaning spending most of the day sitting without whole body movement, have an increased risk of CRC (5). With the turn of the Computer Age, an increasing proportion of Western populations have shifted into occupations requiring less physical labor, which has caused a societal shift to a more sedentary lifestyle, like sitting at an office computer. This is a concern as approximately 80% of a person's day may be spent stationary even with fulfilling the recommended amount of daily physical activity. Pooled epidemiological data has shown a 44% increased risk of colon cancer with high rates of occupational sitting time (4). Similar trends are seen in increased hours of recreational sitting time, like watching television. Overall, higher energy in both work

and leisure time is associated with decreased risk of CRC, in a dose-response relationship.

The etiology behind the inverse relationship of physical activity and CRC is not yet clearly understood. Currently, there a paucity of clinical trials examining this relationship. However, it is likely that the pathophysiology behind the association with increase physical activity and decreased CRC risk and mortality is multifactorial. It is well established that the increased body composition of adipose tissue found in obesity increases overall cancer risk and mortality through increased levels of sex hormones, chronic inflammation, and insulin that promote carcinogenesis (5). Thus, as increased levels of physical activity decrease the rates of obesity, it may also decrease the risk of CRC. Additionally, sedentary lifestyles even in the absence of obesity have been correlated with increased glucose levels and insulin resistance, ultimately leading to high blood circulating levels of insulin (4). Hyperinsulinemia is an independent risk factor for CRC as insulin behaves as a growth factor for cells within the colonic mucosa and has been demonstrated to stimulate colon cancer cells, including stimulating proliferation of metastatic disease (6, 7). Finally, physical activity increases colonic transit time by stimulating the vagal innervation that promotes peristalsis of the intestinal system, which reduces the contact time between food and potential carcinogens with the colonic mucosa, potentially providing an additional protective effect against carcinogenesis (8).

DIET

Healthy dietary habits are essential for maintenance of overall health. Increasing epidemiological research has been focused on how diet affects a multitude of diseases, especially in malignancy. The colon and rectum are particularly susceptible to influence from the diet as it acts as one of the body's first barriers for dietary consumption. Red and processed meat has been faulted as the highest risk foods for increased CRC risk (9). Conversely, there are many proposed protective dietary factors against CRC including fruits and vegetables, fiber, and dairy products, as well as some specific diets and various vitamin supplements. We explore these positive and negative associations in the following section.

Red and processed meat

The typical Western diet consists substantially of processed foods and red meat. Red meat, including beef, lamb, pork, mutton, horse, or goat, is classified as meat from mammalian muscle tissue containing a high concentration of myoglobin (10). When this type of meat undergoes oxidization, it produces oxymyoglobin which appears red, from which the name is derived. When meat products are prepared through salting, curing, fermenting, or smoking before being consumed is it defined as a processed meat (11). Although red meat has significant nutritional benefits, especially regarding its high vitamin and iron content, red and processed meats have been deemed carcinogenic to the human body by the International Agency for Research on Cancer (12). As the gastrointestinal tract mucosa interacts first and foremost with these meats, there has been an abundance of observational data

linking red and processed meats to CRC. The daily meat intake of the average consumer of a Westernized diet is estimated to be around 220g/day (13). It has been demonstrated in systematic reviews of primarily observational studies (14, 15) that diets high in red and processed meats are associated with an increased risk of developing CRC. Increased CRC risk as high as 10–16% has been proposed for each 100g/day increase of dietary red meat and 16–22% for each 50g/day increase in processed meats (14, 15). These trends are supported by experimental studies in animal models (16). However, it is worth noting there is a paucity of experimental studies in clinical research to date and the evidence currently from observational data is highly subjected to other confounding dietary factors. Similarly, in the current data, some results lose significance when evaluating colon and rectal cancers individually (14). Thus, more experimental research is encouraged in this area to truly determine the absolute CRC risk with high red and processed meat intake, but the overall increased cancer risk is undeniable. There has not been any evidence indicating improved mortality with decreased servings of red or processed meat after CRC diagnosis.

White meat, like lean pork and poultry, are not associated with increased CRC risk (17). Therefore, it has been proposed that the heme-containing proteins in the myoglobin rich red meats may promote malignant transformation of epithelial cells in the colonic mucosa through lipid peroxidation, free radical formation, cytotoxicity, and cell hyperplasia (15). Similarly, the process of curing and smoking meat results in the production of carcinogenic compounds like N-nitroso-compounds and polycyclic aromatic hydrocarbons, and cooking meat at high temperatures produce heterocyclic aromatic amines and polycyclic aromatic hydrocarbons (11). These compounds have been linked with increased risk of developing precursor adenomatous colonic polyps that may undergo malignant transformation to develop CRC (18).

Dietary fiber

Diets high in dietary fiber, including whole grains, have been shown to have many health benefits. Whole grains are associated with protective effects against CRC, with 90g/day correlating to a 12–17% decreased risk (9, 19, 20). With each 10g/day of total dietary fiber, a 10–17% CRC risk reduction is observed. This relationship is likely due to dietary fiber decreasing colonic transit time, resulting in decreased exposure to dietary carcinogens, such a processed meats as discussed above. However, it is prudent to note that the evidence for this relationship between dietary fiber and CRC risk is weak.

Pescatarian and other specific diets

Dietary choices are highly influenced by social factors including culture, geography, ethics, and socioeconomic status. A classic comparison in nutrition literature is the Western vs Mediterranean Diets. The Westernized diet refers to a shift towards processed and high fat- and sugar-containing foods, lacking in fresh fruit and vegetables (21). As discussed previously, this type of diet is prone to increased adipose tissue leading to obesity and insulin resistance, which ultimately has been associated with increased CRC risk and worsened CRC survival (5, 6). Conversely, the Mediterranean diet, based on the traditional diet in European countries off the

Mediterranean Sea, consists of whole grains, a variety of fruits and vegetables, low-fat or fermented dairy products, olive oil, and protein sources from fish, white meat, and eggs (21). Other cultural-based diets, including the Healthy Nordic and Traditional Asian diets, or diets designed to improve medical comorbidities like the Dietary Approaches to Stop Hypertension or "DASH" diet, reflect similar composition to the Mediterranean diet. Recent evidence suggests that adherence to the Mediterranean diet is associated with a reduced risk of CRC by 8–17% (22, 23), corresponding to a linear dose-response association of a 4% CRC risk reduction per increasing adherence to the Mediterranean diet (23). No significant associations can be made on CRC-mortality based on current evidence.

Pescatarian diets refer to dietary choices including fish, dairy, grains, fruits, and vegetables, which are similar in composition to the aforementioned diets. Pescatarian diets have been associated with a CRC risk reduction as high as 33% (9). This may be due to the decreased risk in CRC associated with high intake of vegetables and fish. For each increase of 100g/day of vegetable consumption, a CRC risk reduction of 3–10% has been observed (19, 24). Similar results have been seen in the high intake of legumes of 50g/day (9, 24), but the data is conflicted (19, 20). Additionally, high soy intake, which is often a common protein source in vegetarian diets, has some limited data to support a 8–15% reduced risk of CRC incidence (24). On the hand, there is some evidence that high dietary intake of fish of 100g/day has been linked to a 11% decreased risk of CRC development (20), which is supported by some other meta-analysis, but the evidence remains split (24) so only weak recommendations can be made at this time.

Dairy products

Dairy products, including milk, yogurt, butter, and cheese, are a key component for a well-balanced diet as they provide essential nutrients including protein, calcium, and phosphorus. Higher rates of total dairy intake have been linked to decreased incidence of CRC (9). People with high daily intakes of 400g of dairy products per day had an 8–13% reduced risk of CRC, and daily milk intake of 200g/day had a 6–10% reduced risk (20, 25). These inverse relationships have been demonstrated in a dose-response manner and are also demonstrated for cheese (50g/day increments) and fermented milk (200g/day increments) each with a 7% reduced risk of CRC (25, 26). Similar trends have been seen for yogurt consumption (9, 25). This reduced incidence is likely related further data demonstrating a 12% reduced risk of precursor adenomatous and serrated colonic polyps associated with total dairy intake in a dose-response association (27, 28).

There is less overall evidence evaluating dietary dairy intake and CRC-related mortality, but a recent meta-analysis found a 29% reduced CRC-mortality with high total dairy consumption, particularly in the Western population (26). As dairy products act as the primary dietary intake of calcium in most populations, it is purposed that the improved survival is related to calcium intake. This relationship will be further explored in the next section.

Calcium and Vitamin D

Dietary calcium, as described above, is primarily attained through dairy products or alternatively plant-based dairy alternatives. Vitamin D intake is unique as the

metabolism is dependent on both dietary intake and synthesis from skin sun exposure. Intestinal uptake of dietary calcium is aided by vitamin D through the vitamin D receptor in the intestinal cell membranes in the distal small bowel and colon (29). Thus, discussion of the influence of dietary calcium on CRC cannot be completed without the inclusion of vitamin D.

There is strong evidence to support that high dietary calcium intake, deemed at 300–400mg/day, has a significant protective effect in CRC by decreasing risk by 5–6% in a linear dose-response relationship (30, 31). Similarly, vitamin D demonstrates a linear dose-response decrease in CRC risk with each dietary supplementation of 100 units/day by 4%. High levels of the circulating form of dietary or supplemental vitamin D, 25(OH)D, is shown to reduce the risk of colorectal adenoma formation by 20%, with each increase of 200 units/day corresponding to a 10% reduced risk of adenomas (30). This protective effect is amplified when combined with high calcium intake. When both are combined there is evidence of decreasing the risk of adenomatous polyps by as much as 37% and 32% for CRC (30). There has been some additional data showing elemental calcium supplementation of 1200–2000mg/day may decrease the risk of recurrent adenomatous polyps by 23%, with a treatment benefit for each 1 in 20 patients supplemented (32). Furthermore, there is some evidence suggesting that in CRC patients, high levels of circulating 25(OH)D to be associated with improved clinical outcomes and survival, including an improved CRC-specific survival of 35% (30, 33). However, data in this area is still limited.

It has been proposed that calcium and vitamin D work synergistically to protect the colonic mucosa by sequestering fatty acids and bile salts from colonic epithelial cells, compounds that have been indicated to promote carcinogenesis in CRC (34). This in turn may decrease proliferation of the epithelium, reducing colonic toxicity, which may reduce the formation of adenomatous polyps. Additionally, there is evidence to support that calcium may act on mediators along the adenoma-carcinoma sequence during the transformation of pre-cancerous polyps to CRC. Approximately 70% of non-hereditary CRC development is secondary to chromosomal instability that takes place in precursor polyps through mutations in tumor suppressor genes, including the adenomatous polyposis coli gene and KRAS (2). Both calcium and vitamin D have been shown to decrease mutations in the genes mediating this pathway, decreasing the risk of malignant transformation (26, 30). Independently, vitamin D deficiency has been indicated to promote cell proliferation, invasion, metastasis, and angiogenesis, which may reflect the decreased rates of CRC mortality during vitamin D supplementation described above (33). Further mechanisms underlying this relationship is an area of active experimental and epidemiological research.

Folate

Folate, or the supplemental form folic acid, is a B vitamin found in leafy green vegetables and is essential for the prevention of birth defects and can cause significant neurological symptoms in deficient states, more commonly in patients with heavy alcohol use. The current evidence linking folate and CRC risk is conflicting. There is some new data showing a 12% decreased risk of CRC with folic acid supplementation in moderate-heavy alcohol drinkers, but not in the general population (35).

Although there has been some evidence linking a decreased risk of CRC and folate in the general population (9, 24), there remains significant conflicting results (36) so that no association can be made with this current level of evidence.

Vitamin B6

Vitamin B6, or pyridoxine, is a water-soluble vitamin that, when in its active form of pyridoxal 5'-phosphate, acts as a co-enzyme in innumerable metabolic enzymatic reactions (37). There are a few studies to support an inverse relationship between vitamin B6 and CRC risk (9, 24, 37). High intake of vitamin B6 was associated with a 12% decreased risk of CRC (9, 24). There was a dose-response relationship with CRC and the active form of vitamin B6, where CRC risk decreased by 49% for every 100-pmol/mL increase in blood pyridoxal 5'-phosphate level (37). The pathogenesis behind this association may be related to the role of vitamin B6 in the 1-carbon metabolic pathway essential for DNA synthesis and methylation, which in CRC may inhibit carcinogenesis by reducing epithelial proliferation through this pathway (37).

Magnesium

Magnesium, an abundant mineral that is important for many bodily functions, has been implicated to have a protective effect against CRC risk, with a 7% decreased risk for each 50mg supplemented per day (24). Similar results were seen elsewhere (9), with the greatest benefits being observed with supplementation of 200–270mg/day (24, 38). The purposed etiology of this benefit is that magnesium has been shown to be active within cells of the colonic mucosa and may decrease epithelial proliferation through decreased oxidative stress, apoptosis, and inhibition of angiogenesis (38).

Garlic

Garlic is a plant a part of the onion family and typically used to flavor food. Incidentally it also has numerous purposed health benefits, including reduced risk of CRC. The World Cancer Research Fund/American Institute for Cancer Research has stated that garlic may be associated with reduced incidence of CRC with a demonstrated reduced risk of CRC as high as 34–44% for diets high in garlic intake (20). Similar results have been seen elsewhere (39), but conflicting results (24) prevent any strong recommendations. The underlying etiology remains unclear but is purposed to be related to its anti-inflammatory effects on the colonic mucosa which may inhibit proliferation and angiogenesis (39).

OTHER LIFESTYLE FACTORS

Many other lifestyle factors can influence the development and course of CRC. These other lifestyle factors are modifiable and should be identified early in patients who are otherwise high-risk for CRC, to potentially decrease the overall

risk of CRC incidence. Upon CRC diagnosis, these professionals within the healthcare team should reassess for the presence of these factors to aid in cancer survival.

Coffee and other caffeine sources

Dietary coffee, tea, and other caffeinated beverages are highly prevalent in most diets. The evidence is unclear whether regular intake of these beverages affects CRC risk. Recent meta-analyses were unable to show an association between coffee consumption and CRC risk (20, 40), although there is some conflicting evidence in this area an older meta-analysis reported a dose-response relationships of 3–6% reduced CRC risk per 1 cup of coffee per day (41). There is similarly conflicting evidence regarding tea consumption and CRC risk (24). Overall, associations can be made definitively at this time due to the weak evidence.

Tobacco

The overall poor health effects from tobacco and cigarette smoking are well established and undebatable. Tobacco use is an established risk factor for CRC incidence and prognosis. Both previous and current cigarette smoking is associated with an increased risk of CRC at 17–25% (42, 43). This increased incidence is likely secondary to an increased risk of both adenomatous and serrated polyps with cigarette smoking (43). The carcinogens contained in cigarette smoke, including polycyclic aromatic hydrocarbons and heterocyclic amines among others, cause DNA mutations of mediators in the adeno-carcinoma sequence through carcinogen-metabolizing enzymes (44). Compared to never smokers, there was also an increased risk of mortality with CRC in former and current smokers at 15% and 40%, respectively. An increase in cigarette consumption of 1 pack (or 20 cigarettes) per day increased the risk and mortality of CRC to 17% and 40%, respectively, in a dose-response relationship (42). Therefore, smoking cessation should be heavily encouraged for all patients, but particularly high-risk for CRC and current CRC patients.

Alcohol

Increased alcohol consumption has been indicated in the increased risk of several different malignancies, including CRC. For each increase in total alcoholic drinks per day, defined as 10g/day, CRC risk increases by 6% (20). The risk with moderate (2–3 alcoholic drinks/day) and heavy (more than 4 alcoholic drinks/day) was associated with an increased risk of 21–52% (24, 45). There is sufficient evidence to say that heavy alcohol intake is a strong modifiable risk factor for CRC development and worsens both CRC and overall health outcomes (9). The current evidence demonstrating the effects of alcohol use on CRC mortality is controversial, but the consensus is to recommend the avoidance of moderate-heavy alcohol consumption in the context of cancer diagnosis as it may impair the efficacy of cancer treatment (46).

A summary of the current evidence linking these lifestyle modifications and CRC risk and morality is provided below in Table 1.

TABLE 1 Summary of associations between lifestyle exposures on CRC incidence and mortality

Exposure	Overall Effect	CRC Incidence	CRC Mortality	Level of Evidence
Daily physical activity	Protective	20% relative risk reduction (3, 4)	42% improved all-cause and cancer-specific mortality (3)	Moderate
Sedentary Lifestyle	Harmful	44% increased risk of CRC (4)	NED	Moderate
Red and processed meat	Harmful	16% increased risk per 100g red meat/day (12) 22% increased risk per 50g processed meat/day (12)	NED	Strong
Dietary fiber	Protective	10–17% decreased risk per 10g/day (9, 16, 17)	NED	Weak
Mediterranean Diet	Protective	8–17% decreased risk (19, 20)	NED	Weak
Pescatarian Diet	Protective	33% decreased risk (9)	NED	Weak
Dairy	Protective	8–13% decreased risk per 400g/day	29% reduced CRC-mortality (23)	Moderate
Calcium	Protective	6% decreased risk per 300-400mg/day (27, 28)	NED	Moderate/ Strong
Vitamin D	Protective	4% decreased risk per 100units/day	35% improved cancer-specific survival (27, 30)	Moderate
Folate	Protective*	12% decreased risk in heavy alcohol users (32)	NED	Weak
Vitamin B6	Protective	12% decreased risk (9, 21)	NED	Weak
Magnesium	Protective	7% decreased risk per 50mg/day	NED	Weak
Garlic	Protective	34–44% decreased risk (17, 36)	NED	Weak
Coffee	U	NED	NED	Weak
Tobacco	Harmful	17–25% increased risk (39, 40)	40% increased mortality per pack of cigarettes/ day (39)	Strong
Alcohol	Harmful	6% increased risk with each 10g/day (or one alcoholic drink) (17, 21, 42)	Unclear association. Current literature is mixed.	Strong

NED, Not Enough Data

*Controversy of overall benefit unclear in general population based on current evidence. Harmful exposures, including sedentary lifestyles, red/processed meats, tobacco, and alcohol, are well established in the literature, and accepted into clinical practice. On the other hand, the protective factors listed above still require further evaluation to produce stronger evidence to influence current medical recommendations.

CONCLUSION

Physical activity, diet, smoking, and alcohol intake are all modifiable lifestyle factors that can influence both CRC incidence and survival. The prudent healthcare professional should evaluate patients at high-risk of CRC from genetics or medical comorbidities and provide counselling to patients on these lifestyle behaviors. Ongoing epidemiological studies are required to further elucidate the relationship of some dietary and supplement factors on the protective benefit on CRC risk and mortality. Many of these supplements do not currently have strong enough evidence to be implemented into standard medical practice. Overall, the cornerstone of lifestyle modifications for CRC involves promoting an active lifestyle with a well-balanced diet and moderating or eliminating the intake of processed meats and alcohol.

Conflict of Interest: The authors declare no potential conflict of interest with respect to research, authorship and/or publication of this chapter.

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