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Review

# Role of Diet in the Pathogenesis of Colorectal Polyps and Cancer

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**Abstract**

Colorectal cancer (CRC) is currently the third most common cancer within the United States among both males and females, with increasing rates occurring in younger individuals compared to the past. Multiple environmental and social aspects including diet may be contributing to this increase in CRC rates. The aim of this review is to examine foods containing high fructose corn syrup, processed meats, and red meats which have shown to be linked to an increase in incidence of CRC. These foods can be a cause for disruption in a healthy microbiome leading to dysbiosis, which can have downstream effects on CRC formation. With the current data showing evidence of potential triggers and associations leading to CRC, more

studies are needed to help directly link these dietary components and their pathways to cancer formations.

**Keywords**
Diet; nutrition; colorectal cancer; neoplasia; polyps; high fructose corn syrup; processed meats; red meats; dysbiosis; surveillance screening; microbiome

## 1. Introduction

There is growing evidence that specific dietary components may play a major role in the development of various metabolic diseases and cancer. The incidence of colon cancer has been increasing in younger individuals with smoking, alcohol, and sedentary lifestyle all being cited as risk factors [1]. Recent evidence has shown dietary components and behaviors may also play a large role in the development of colorectal cancer (CRC) [2]. This chapter will focus on recent studies showing an increase in dietary intake of high fructose corn syrup (HFCS), red and processed meats, and the role of the gut microbiome on colorectal polyps and CRC.

Colorectal cancer is the 3rd most common cancer in both men and women within the United States [3]. With increased screening rates with colonoscopy there seem to be decreasing rates of CRC in people greater than 65 years old; however, rates in people less than 65 seem to be increasing [3, 4]. For example, a study done between 1974 and 2013 demonstrated, in an age-period cohort analysis, a trend for increasing risk of CRC in birth cohorts of adults younger than 50 years [5]. This trend has prompted the US Preventive Services Task force to recommend offering CRC screening for all asymptomatic adults without risk factors starting at age 45, reduced from the prior recommendation of age 45 for African Americans and age 50 for all others, which represents a significant change in the scope of CRC screening [6].

A recent study found that the incidence of CRC in young adults in nine high income countries, including the US has increased in the last 20 years. The pattern found was sharp in contrast to the rapid declines found in older adults [7]. One of the factors that may be playing a role is obesity, which in the setting of its rising prevalence in young adults was found to be associated with an increased risk of early onset CRC among women [8]. Researchers have set out to explain the drastic increase, and evidence of this increased incidence has been suggested to revolve around human environmental changes such as smoking, alcohol use, decreased physical activity, changes in diet such as increased consumption of red meat and processed foods and decreased intake of dietary fibers [9].

Another important factor to take into account is the colon microbiome, which may also be playing a role in the pathogenesis of CRC in younger patients, as bacterial composition demonstrates both a proximal-distal gradient as well as a luminal-mucosal gradient. Factors affecting this composition continue to be an active area of investigation, and may include diet, aging, sleep, and other environmental exposures [9, 10]. For instance, a recent study in mice demonstrated that *Fusobacterium nucleatum* presence is involved in metastasis from primary colorectal tumor. Furthermore, tumors associated with *F. nucleatum* presence were responsive to antibiotic treatment and demonstrated decreased bacterial load, cancer cell proliferation, and tumor cell

growth [11]. Observations like this one, have prompted researchers to investigate the microbiome's role in carcinogenesis and carries implications for future therapeutic options for CRC, including antibiotics, probiotics, and stool transplantation [12].

## 2. High Fructose Corn Syrup and CRC

Dietary sugars have been a focus of interest as high intake has been associated with the development of obesity, diabetes, and cardiovascular disease [13, 14]. High fructose corn syrup is the processed form of corn starch that contains free fructose and glucose. It has replaced the use of naturally found sugars in the United States due to its relatively low cost and flavor profile. The diverse utility allows it to be used in a variety of consumer goods ranging from canned foods, cereals, sweetened beverages, and fast-food products [13]. While the relationship between HFCS and cardiovascular health has been an area of focus, only recent data has shown a relationship between HFCS to colon polyps and CRC.

Mechanistically, most glucose absorption occurs in the small intestine enterocytes through the sodium-glucose co-transporter and a glucose transporter type 2 (GLUT2) mechanism [15]. The fructose pathway, however, is mediated by a passive transporter through GLUT5, also present in epithelial enterocytes. It has been demonstrated that as little as 5 g of fructose can overwhelm this passive transporter [16]. Rather than being absorbed, this luminal fructose burden instead gets delivered downstream to the colon, where it can be consumed by local flora, primarily in the right colon [17]. Many studies have begun to show that cancerous tissues have a higher expression of GLUT5 transporters, including CRC tissue [18].

In 2019, Gonclaves et al. [19] investigated the effect of HFCS using a mouse model. They compared adenomatous polyposis coli (APC) positive mice and administered daily HFCS compared to control mice. They administered to the mice 20 g of weight-adjusted HFCS, a human-dose equivalent of 1 soda a day. They found that those with HFCS had a large increase in tumor size and grade even in the absence of obesity and metabolic syndrome [19]. This uptake of fructose caused an effect through accelerating glycolysis and de novo lipogenesis. Although the pathogenesis and exact mechanisms are still being elucidated, the studies have shown that adding fructose to CRC cells grown in hypoxic environments allows those cells to survive longer than cells without fructose. This may be in part because the fructose was absorbed through the GLUT5 fructose transporter and then retained by the tumor cells. This leads to a shift of products throughout the glycolytic pathway and increased fatty acid metabolism to support tumor growth.

Furthermore, a key protein involved throughout the mechanism is pyruvate kinase M2 (PKM2) as studies have shown that when fructose is inhibited from binding to PKM2, colorectal cells and villi have poorer growth and metabolic activity [20]. The study was able to identify ketohexokinase (KHK) as an important key accelerator in tumor growth and may be an important target for future studies looking at therapeutic targeting in KRAS-mutant CRC [19]. KHK is a fatty acid synthesis enzyme that when inhibited, showed tumor growth is limited or decreased compared to uninhibited models and they could not utilize the fructose available. The above findings have been in mouse models, but offer compelling biochemical evidence that dietary mechanisms play a large role in CRC tumorigenesis and further studies are needed to define the suspected application in human models.

Prospective data shows an incremental cancer risk in the population. Joh et al. [21] evaluated development of early-CRC based on dietary trends and age. They prospectively analyzed 33,106

participants who provided their dietary intake behaviors during adolescence to determine the effects of high consumption of simple sugar and HFCS containing sweetened beverages [21]. There was an increased risk of 1.17 (95% CI, 1.05-1.31) for all adenomas and 1.30 (95% CI, 1.06-1.60) for high-risk adenomas. By location, the highest risk was for rectal adenomas, with an associated risk rate of 1.43 (95% CI, 1.10-1.86) [21].

Another study of 95,464 participants conducted by Hur et al. [22] looked at an associated risk between sugar-sweetened beverages (SSBs) and CRC. Compared with individuals who consumed less than 1 serving per week of SSBs in adulthood, women who consumed more than 2 servings per day had a more than doubled risk of CRC with a 16% higher risk per serving per day increase. Each serving per day increment of SSB intake in adolescents (13-18 years) was associated with a 32% increased risk of early-onset CRC. Furthermore, replacing each serving per day of SSB with other beverages (e.g. coffee or milk) in adulthood was associated with a risk reduction for early-onset CRC of 17-36% [22]. Further research studies are needed to determine exact mechanisms, but the above data offers a compelling argument that dietary modification at a systemic level is needed to battle the growing CRC trends across western countries.

Similarly, to the data emerging on colorectal polyps and CRC, studies have looked specifically into the colitis-associated diseases and their relationship to HFCS. Long standing gastrointestinal inflammatory disorders such as inflammatory bowel disease (IBD) (i.e. Crohn's disease or Ulcerative colitis) increase the risk of CRC through long-standing inflammatory states [23]. Nishiguichi et al. [24] found procolitic effects of a high fructose diet could be reversed by switching mice to a control diet and thereby prevented a high fructose diet-induced worsening of acute colitis likely from similar mechanisms as mentioned above. Thus, by reducing chronic inflammation of disease states such as IBD, reducing fructose in the diet could be protective against colitis-associated cancers. Further studies should help elucidate the exact mechanisms involved.

## 3. Processed Foods, Red Meats, and CRC

The first major push that red meats and processed meats could be related to increased rates of CRC was the "Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective", by the World Cancer Research Fund/American Institute for Cancer Research [25]. The report showed approximately a 37% increased risk of colon cancer for every 100 g/day increase in red and processed meats [25]. This was shown again in 2011 by Chan et al. [26] who was able to find similar data points by comparing studies from 1966-2011 with red meat and processed meat intake. The data showed an increase in CRC risk of about 14% for every 100 g/day increase of total red and processed meat intake and 25% increased risk for colon cancer [26]. The International Agency for Research on Cancer (IARC) in 2015 labeled red meats as "potentially carcinogenic" and processed meats as "carcinogenic" due to its effect on increased CRC [27]. More recently, a systematic review and meta-analysis of 148 prospective studies showed that processed meat consumption was significantly associated with a 21% greater colon cancer risk and total red and processed meat consumption was significantly associated with greater risk of colon cancer (RR = 1.21; 95% CI = 1.09 - 1.34) [28]. The processes to prepare and create processed foods lead to the potential sources of causing inflammation and biologic changes which increase the risk for malignancy formation.

The possible biologic mechanisms of red meats leading to cancer are heterocyclic amines (HCA), heme compounds, and N-nitroso compounds (NOC). HCAs, which are considered potential

carcinogens, are produced when amino acids within the meat are cooked at very high temperatures [29]. Heme products within the meat have been shown to induce epithelial damage within the colon of mice [30], which leads to hyperproliferation of epithelial cells within the intestinal crypts [31]. Van Der Meer-Van Kraaij et al. [32] demonstrated in mice that heme products within the colon led to down regulation of pentraxin, a protein involved in inhibiting cellular apoptosis. Both of these pathways in mice show processes that heme products can directly and indirectly lead to formation of CRC by inducing uncontrolled growth. NOCs can act as DNA alkylating agents [33], which can lead to mutations promoting cellular growth and division [34]. Proteins from the meat can cause formation of hydrogen sulfide, ammonia, secondary bile acids, and phenolic compounds, which can all increase the risk for CRC [35]. Hydrogen sulfide which is produced mainly from large meat diets coming from mainly sulfur containing amino acids and preservatives with inorganic sulfur [36]. Sulfur metabolism can lead to disruption of mucus bilayer [37], which in turn can lead to DNA damage and inflammation [38]. A recent study with large prospective cohorts with relatively high rates of follow-up over 25 years found that long-term adherence to sulfur-based diets was associated with increased rates of CRC [39]. Dermadi et al. [40] showed that mice fed western diets, had a decrease in a specific intracellular bile acid transporter, FABP6, and these mice were found to have increased rates of CRC due to overall decreased rates of bile acid transport. The proposed mechanism was an overall disruption of lipid metabolism and bile acid transport which led to a decrease in the Farnesoid X receptor (FXR) which is a key protein involved in bile acid homeostasis [41]. FXR deficiency has been seen to increase intestinal cell proliferation and inflammation in murine models and leading to carcinogenesis [42].

## 4. Protective Foods/Minerals Against CRC

Vitamin D – Vitamin D is known as a fat-soluble vitamin which is produced from ergocalciferol and cholecalciferol, which can be found in some fortified foods, ultimately leads to the production of calcitriol. Vitamin D has been hypothesized to reduce overall risk of cancer, given the regulation of calcitriol in multiple signaling pathways involving proliferation, apoptosis [43], and angiogenesis [44, 45]. Calcitriol leads to reduction in proliferation from multiple mechanisms including down regulation of cyclin-dependent kinases (CDK), induction of CDK inhibitors [46], leading to growth arrest, and interfering with proliferative signaling pathways involving epidermal growth factor [47], and insulin like growth factor II [48, 49]. Observational studies have shown people with CRC tend to have increased rates of vitamin D deficiency. A study of over 115,000 female patients, from age 25 to 42 from 1991-2015, showed that increased vitamin D within the diet, led to decreased rates of early on-set CRC [50]. Similarly, it has been seen in other studies that higher circulating levels of 25-hydroxy vitamin D in women compared to women with lower levels have a lower risk for CRC [51].

Fiber – Fiber is defined as plant material composed of cellulose, lignin and pectin. The primary proposed mechanisms for reduction of CRC are reducing fecal transit times and diluting the potential carcinogens thus reducing carcinogens binding to the gastrointestinal epithelium and maintaining the cell integrity [52]. Other proposed mechanisms are absorption of heterocyclic amines which affects overall bile acid metabolism [53] and increasing stimulation of anaerobic fermentation of the gut flora leading to increases in short-chain fatty acids (SCFAs), which are protective against CRC. Early observational studies showed an initial protective association between increased fiber intake and reduction in CRC [54, 55]. In the past fiber intake was measured by overall

intake of fruits and vegetables [56, 57]. More recent data has been trying to isolate specific foods which are high in fiber and in the overall diet of most people. A recent meta-analysis found increasing consumption of whole grains, which consistent up to 7-15% fiber, from 15 g to 90 g/day led to up to 17% reduction in CRC [58]. There has been some data showing fiber and CRC might not have a specific association [59-61]. However, recall bias, selection bias, and sample size can lead to discrepancies between earlier case control and cohort studies [52]. Some attempts to reduce these discrepancies have been attempted such as with Dahm et al. [62] who had participants use food diaries to reduce the amount of recall bias, which showed intake of fiber was inversely associated with CRC. Overall, more data are needed, ideally from randomized control trials, to conclusively state if fiber is inversely associated with CRC.

Flavonoids – Polyphenols are a group of compounds found in several plant foods and drinks, including teas, vegetables, and fruits. Flavonoids, a class of polyphenols, have a demonstrated anti-inflammatory role explored in various conditions, including inflammatory bowel disease [63-65]. Their presence has been theorized as a potential reason for the protective effect of these foods and beverages in preventing various inflammation-mediate conditions, including malignancy. In-vitro and in-vivo models have also demonstrated an association between flavonoid intake and decreased carcinogenesis. One proposed mechanism for this effect is through effect on the commensal flora. Polyphenol intake has been associated with an increase in abundance of flora that produce SCFAs. Polyphenol intake also has direct effects on the intestinal mucosa and on barrier function. Several polyphenols, including those found in green tea, inhibit NFkB production and subsequently inhibit cyclooxygenase and inducible nitric oxide synthase production, thus decreasing the local inflammatory response [66]. An in-vitro analysis demonstrated decreased malignant conversion with the use of a bacterial flavonoid metabolite, 3,4-dihydroxyphenylacetic acid on cell lines treated with hemin, a carcinogenic metabolite of myoglobin [67]. Polyphenol metabolites, including epigallocatechin-3-gallate have demonstrated increase in the pro-apoptotic pathway, specifically through induction of p53 and caspases [68]. While polyphenol use has been explored for potential protective effects against CRC, their use has also demonstrated potential as an adjunct to chemotherapy and radiation therapy. Quercetin, a flavonoid found in many vegetables, has demonstrated increased effect of chemoradiation on CRC cells in-vitro [69]. Combination use of curcumin, a polyphenol found in turmeric, with traditional chemotherapy has demonstrated increased anti-tumor effect in prostate cancer cell lines [70]. While in-vitro and in-vivo studies have been promising, clinical trial data are needed to inform the preventative and therapeutic roles of polyphenols through.

β-Hydroxybutyrate (BHB) – BHB is a ketone body, which is used by the body for energy transfer in times of carbohydrate restriction, fasting, and during prolonged exercise [71]. BHB acts on a variety of different signaling pathways notably for hydroxycarboxylic acid receptor 2 (HCAR2), a surface G coupled receptor. HCAR2 activation within the gut epithelium leads to overall stabilization of the integrity of the gut membrane [72] and activation of the NLRP3 inflammasome [73] which has shown in mouse models to reduce colitis [71]. A recent study done by Dmitrieva-Posocco et al. [74] investigated the role of BHB and CRC via the activation of HOPX a negative regulator of tumorgenicity [75]. HPOX deficient mice did not respond to BHB, however the wild type models had decrease in tumor burden [74]. BHB was also shown to decrease growth of tumors in human cell lines that expressed both HCAR2 and HPOX [74]. While more studies are needed to confirm this in

clinical trials, this shows promise for another avenue on preventing CRC and possibly using diet in conjunction with surgery and chemotherapy as an avenue for treatment of CRC.

## 5. Microbiome/Dysbiosis and CRC

The gut microbiome is a complex environment of various microorganisms and contains over 7000 different strains of bacteria [76]. It plays a large role in metabolism as well as communicates with the brain and immune system. Dysbiosis, caused by factors such as stress, diet, medications, and comorbidities, is implicated in a vast variety of chronic diseases, including inflammatory bowel disease and cancer. While the role of the microbiome in the development of colorectal carcinoma is not fully understood, there are several bacteria known to be significantly involved. *F. nucleatum* has been found in increased prevalence in adenomas and CRC, as well as metastasis of CRC [77]. *F. nucleatum* promotes CRC development through a multitude of pathways. In addition to invasion and release of proinflammatory cytokines from host cells, it inhibits apoptosis of infected cells via miRNA expression [77], inhibits $CD4^+$ T cells to reduce antitumor immune response [78], and upregulates the Wnt pathway to promote growth of CRC cells [79]. *Bifidobacterium* and *Faecalibacterium prausnitzii*, on the other hand, have demonstrated anti-inflammatory properties and have specifically inhibited the development of preneoplastic lesions in chemically induced CRC [80]. Dysbiosis of these specific bacteria have been consistently reported in patients with CRC compared to health control groups [81]. Recent literature has studied the microbial ratio in hopes of identifying a biomarker for screening early CRC. The ratio of *F. nucleatum/Bifidobacterium* was found to have a sensitivity of 84.6% and a specificity of 92.3% in detecting CRC, and in combination with *F. nucleatum/F. prausnitzii*, detected 90.0% sensitivity and 60.0% specificity in detecting stage 1 of CRC [82]. With the knowledge that *F. nucleatum* displays strong antagonistic activity towards *Bb* and Fp, the negative correlation seen in CRC fecal samples is unsurprising.

Evidence of the above shifts in microbiome offers a potential opportunity for probiotic intervention. One study examined the effect of probiotics on the microbiota in patients with CRC and found a significant difference in microbiota diversity and alterations in the mucosa. When compared to placebo, the use of probiotics such as *Bifidobacterium longum, Lactobacillus acidophilus,* and *Enterococcus faecalis*, was shown to have a 6-fold decrease in relative abundance of *Fn* [81]. An additional study examined the use of heat-killed *Lb* and its effects on *Fn* virulence factors in oral flora. They discovered a decrease in Fap2 virulence factor expression and subsequent host cell adhesion in the presence of heat-killed *L. acidophilus* [83]. Not only does this help prevent *F. nucleatum/*invasion and release of proinflammatory cytokines, but Fap2 has been recognized as a galactose-binding lectin. Notably, colorectal adenomas express high levels of Gal-GalNAc lectin, the Fap2 virulence factor which plays a large role in recruitment of *F. nucleatum* [83]. Although this study examined the effects on oral *F. nucleatum*, it should be considered that over 40% of patients with CRC exhibited identical strains of oral and CRC specimens, thus suggesting similar efficacy with colorectal *F. nucleatum* [84]. While studies show benefit in probiotic use against *F. nucleatum* CRC, further research is required to determine their use in prevention and treatment.

More broadly, pre- and pro- biotic foods have been explored to modify the risk of CRC. Fermented foods, especially yogurt, have been of particular interest due to their demonstrated effect on the composition of the colonic microbiome [85, 86]. While the overall microbiome effects of specific fermented products vary, yogurt consumption has been associated with decreased risk

of several cancers [86, 87]. A large meta-analysis has demonstrated that high yogurt consumption is associated with low colon cancer risk [88].

## 6. Conclusion

With multiple factors playing a role into the formation of CRC, diet and gut health has emerged as an important component with a need to focus on changes earlier in life to decrease the overall risk of CRC. This is important as younger individuals are showing increased rates of CRC. Clearly, more protective interventive measures are indicated as possible mitigation strategies for protection. The ideal way would be eliciting dietary changes early in life, thereby potentially decreasing risk factors for CRC. Notably this would emphasize avoiding a fully "westernized diet" (characterized by proteins mainly from red and processed meats, saturated fats, corn-derived fructose syrup, and decreased amount of fruits and vegetables) [89]. Moving towards diets such as the Mediterranean diet, and plant-based meats could be healthier alternatives to reduce the chemicals which affect the gut microbiome in a favorable direction "Protective foods" in a diet such as fiber, fruits, vegetables, vitamin D, dairy products and fish products have shown to have risk reduction against CRC [90]. These foods have been shown to increase the biodiversity of the microbiota and reduce the incidence of more pathogenic bacteria. Clearly national guidelines have emphasized that earlier surveillance which has already been implemented with the change of routine colonoscopy for CRC screening shifting to the age of 45 from 50 [6]. Large strides in the reduction of the incidence of CRC has been made over the past decades and is important that expanding efforts to reduce the risk for the general population that may be exposed to the ramifications of a western diet.

## Author Contributions

Dr Johnson DA contributed to the construction of the project; all authors wrote and edited the manuscript.

## Competing Interests

The authors have declared that no competing interests exist.

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