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Review

Colorectal Cancer Risk Factors: Insights into the Significance of Modifiable Environmental and Nutritional Lifestyle Factors

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ABSTRACT

In the world, colorectal cancer (CRC) ranks second in terms of cancer-related deaths, is the most common cancer in both men and women and is the primary cause of death from gastrointestinal cancer. People with inflammatory bowel conditions, like Crohn's disease and ulcerative colitis, should be closely watched because they have a higher risk of CRC. There are hereditary and environmental risk factors for CRC. Additionally, the risk of developing CRC is increased by smoking, eating habits, aging, genetic factors, intestinal inflammatory disease, and polyps. More intriguingly, a higher risk of CRC has been linked to modifiable environmental factors and modifiable nutritional factors, such as eating a high-fat diet, consuming red and processed meat, and consuming low amounts of fiber and vitamin D. We reviewed the published significance of risk factors on colorectal cancer focusing on environmental risk factors and nutritional risk factors to provide protective suggestions to minimize the occurrence of CRC.

Keywords: Colorectal Cancer; Risk Factors; Environmental Factors; Nutritional Factors.

1-Introduction:

One of the most prevalent cancers in the world is CRC. It comes in second for cancer-related deaths and third for incidence (1). One of the most common cancers in the world, CRC, accounted for nearly 10% of all new cancer cases and deaths globally in 2018 with 1.8 million new cases and 881,000 reported deaths (2). It is estimated that there were over 1.9 million new cases of CRC in 2020, making it the third most diagnosed cancer globally (3). In 2035, there might be close to 2.5 million new cases. The USA's statistics show that the quick advancement of screening and treatment procedures has resulted in a ~50% decrease in the death rate from 29.2 per 10,000 patients in 1970 to 13.7 per 10,000 patients in 2016. Nevertheless, it appears that only highly developed nations are seeing this tendency. (4). In the meantime, the 5-year survival rate for metastatic CRC is 12%, while the 5-year survival rate for CRC is approximately 64%. More research is still needed to create efficient medical intervention strategies (5).

2. Epidemiology

An estimated 132,700 new cases of CRC were reported in the United States in 2015, according to the Surveillance and Epidemiology program (6). At 8.1 deaths per 100,000 people, CRC is expected to claim 49,700 lives, accounting for 8% of all new cancer cases. This largely affects developed regions (25.1/100.000 inhabitants), whereas undeveloped regions (3.9/100.000 inhabitants) have a much lower rate of this. Nonetheless, a steady decrease in the frequency has been noted, which corresponds with the rise in early identification through colonoscopy and the excision of precancerous lesions in adults between the ages of 50 and 75 (7,8).

In the US, the odds of developing invasive CRC are 5% for men (1 in 20) and 4.6% for women (1 in 22). The median age at diagnosis is approximately 70 years old. The incidence of colorectal cancer varies greatly throughout the world; in the US and Europe, it is ten times higher than in African and Asian nations (9). Western lifestyle, with its known risk factors of red meat (beef and pork), alcohol consumption, and obesity, is associated with a higher risk of CRC (10). Individuals who suffer from inflammatory bowel diseases, such as Crohn's disease and ulcerative colitis, are also at an increased risk of colorectal cancer and should be closely monitored (11). Five percent of cases of CRC are caused by hereditary syndromes known to be

linked to the disease's development, such as familial adenomatous polyposis (FAP) and hereditary non-polyposis CRC (HPNNC). Another twenty percent of cases are thought to be related to familial clustering. The majority of CRC cases—roughly 75%—are sporadic (12).

3. Risk Factors

Factors such as endometrial, colon, rectal, ovarian, breast cancer, diabetes mellitus, history of ulcerative colitis, Chron's disease, and personal history of polyposis are linked to a 30–50% increased risk of developing CRC. All of these risk factors are linked to approximately 75% of malignant tumors of the colon and rectum. It's arguable whether hyperplastic polyposis and cancer are related. Adenomatous polyps are more common in adults over 50, but most of them do not turn into cancer. Its clinical significance is determined by its size and histology (13).

In hyperplastic polyps, dysplasia, the right colon location, and polyp sizes of 10 mm or greater are risk factors for cancer. a mixed polyp hyperplastic-adenomatous adenoma within the polyp, defined by a family history of colon cancer and more than 20 hyperplastic polyps in the colon. There is a mild dysplasia that, due to genetic changes, escalates to a moderate or severe degree within a well-defined time frame of ten to fifteen years. The hematic or lymphatic dissemination pathways determine the rate of growth and the length of time the disease progresses; however, surgical manipulation after a laparoscopic colectomy has been reported in some cases (13).

Male sex and advancing age have continuously demonstrated high correlations with the incidence of disease in epidemiological research. CRC can occur as a result of both environmental and inherited risk factors. Of all patients with colorectal cancer, roughly 10–20% appear to have a positive family history (14), with variable risk based on the number and severity of afflicted relatives as well as the age at which colorectal cancer was discovered (15). The heritability of colorectal cancer is estimated to be between 12% and 35% based on twin and family studies (16).

The two categories of hereditary CRC syndromes are polyposis and non-polyposis (including Lynch syndrome and familial colorectal cancer). When a doctor is alerted by the amount of polyps, the polyposis syndromes are easier to identify (17). The right diagnosis may be determined only by the type of polyps. Despite the fact that Lynch syndrome patients

sometimes go undiagnosed because their adenomas are few and anatomically similar to random lesions (18). Patients of any age or a subgroup of those under 70 years of age are currently undergoing a systematic molecular analysis of tumor tissue to aid in the diagnosis of this genetic syndrome. Molecular analysis is used to identify microsatellite instability (MSI), which is the outcome of microsatellite regions in the tumor growing or shrinking relative to healthy tissue. A malfunction in the DNA mismatch repair system is the cause of Lynch syndrome (19). Furthermore, these tumors lack mismatch repair proteins, according to immunohistochemistry. However, MSI is not specific to Lynch syndrome; approximately 15% of colorectal cancers that arise spontaneously also show signs of MSI. From the age of 20 to 25, patients with Lynch syndrome are recommended to undergo frequent, yearly colonoscopies due to the accelerated adenoma-carcinoma pathway (20-23).

The risk of CRC is increased by many environmental lifestyle factors that are largely modifiable, including smoking (24), drinking too much alcohol (25), gaining weight (26), and consuming red and processed meat (27). While obesity and physical inactivity are two risk factors that are common to both type 2 diabetes and colorectal cancer, people with type 2 diabetes still have an elevated risk even after adjusting for these variables (28). According to research on colonic microbiota, some bacterial species, like Bacteroides fragilis and Fusobacterium nucleatum, may increase the risk of colorectal cancer (29, 30) (Figure 1).

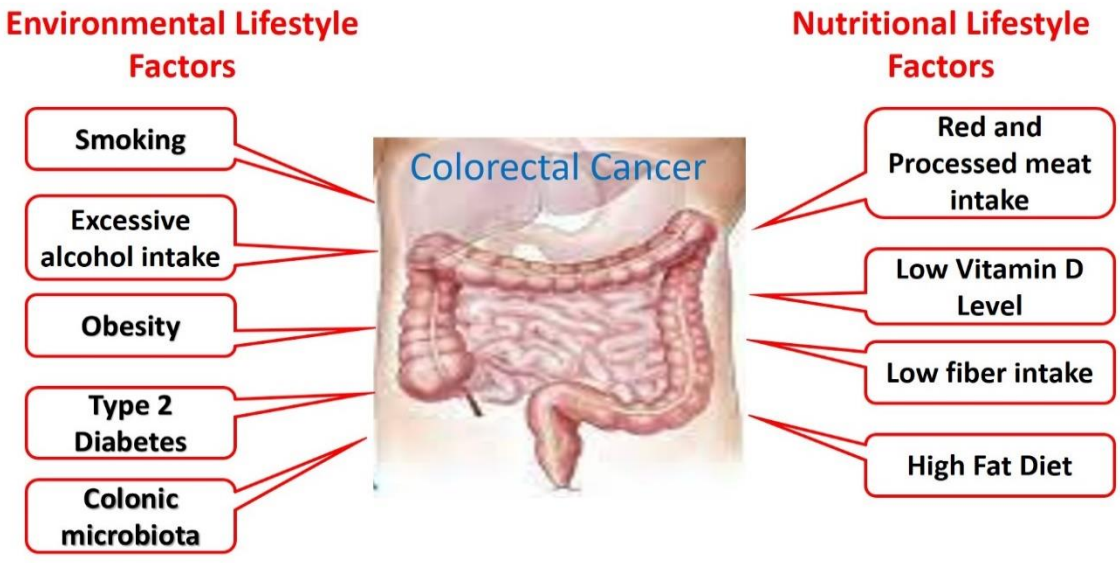

Figure 1: List of modifiable Environmental and Nutritional risk factors for colorectal cancer

3.1. Modifiable Environmental lifestyle factors

3.1.1 Smoking

Smoking has been associated with an increased risk of CRC (24). The link between smoking and colorectal cancer is supported by evidence from epidemiological studies, which have consistently shown that individuals who smoke are at a higher risk of developing colorectal cancer compared to non-smokers (31). Smoking has been identified as a modifiable risk factor for CRC. Individuals who smoke have a higher risk of developing both colon and rectal cancer (32). The risk of colorectal cancer is often associated with the duration and intensity of smoking. In other words, the more cigarettes smoked over a more extended period, the higher the risk may be (33).

The biological mechanisms underlying the association between smoking and CRC are not fully understood, but several hypotheses exist. Smoking is known to introduce various carcinogens into the body, and these substances may play a role in the development of CRC. Numerous harmful and cancer-causing substances, including heavy metals, alkaloids, aromatic amines, phenolic compounds, PAHs, and TNSAs, are found in cigarette smoke (34, 35). Furthermore, Li LF et al. (2014) reported a number of potential pathways, such as the activation of nicotinic acetylcholine receptors (nAChRs), creation of DNA adducts, stimulation of tumor angiogenesis, engagement of the immune system, and others, may contribute to the GI tract tumorigenesis caused by these harmful and carcinogenic ingredients. These mechanisms typically coexist and work in concert to promote carcinogenesis. Nicotine, for instance, can activate the nAChRs on cancer cells and cause the release of growth factors into the tumor microenvironment, such as IL-1β and vascular endothelial growth factor (VEGF), which can increase tumor angiogenesis and subsequently promote tumor growth (36).

Also, Smoking may also influence the progression of CRC. It has been suggested that smoking could be associated with more aggressive tumor behavior and poorer outcomes in individuals with CRC (37). The risk associated with smoking may interact with other risk factors for CRC, such as diet, physical activity, and family history. Therefore, a comprehensive understanding of an individual's risk profile involves considering multiple factors (38). One positive aspect is that the risk of CRC appears to decrease after smoking cessation. However, it may take several years for the risk to approach that of non-smokers (39).

3.1.2. Excessive alcohol intake

Studies have demonstrated that excessive alcohol intake is associated with an increased risk of CRC. Numerous epidemiological studies have consistently shown a positive association between excessive alcohol consumption and the risk of CRC (25). Similar to smoking and CRC, there appears to be a dose-response relationship between the amount of alcohol consumed and the risk of CRC. Higher levels of alcohol intake are associated with an increased risk (40). Pedersen A. et al. (2003) have stated that the type of alcoholic beverage may also play a role. While the evidence is not entirely consistent, some studies suggest that the risk may be higher with the consumption of spirits (hard liquor) compared to beer or wine (40).

Moreover, the biological mechanisms through which excessive alcohol consumption may contribute to CRC are not fully understood. However, it is believed that alcohol and its metabolites may have direct toxic effects on the cells lining the colon and rectum, leading to the development of cancer. Acetate and acetaldehyde are the two main metabolites of ethanol. The liver's alcohol dehydrogenase (ADH) enzymes first convert ethanol to acetaldehyde. To a lesser extent, the enzymes catalase and cytochrome P450 2E1 (CYP2E1) also aid in the oxidation of ethanol. Aldehyde dehydrogenase (ALDH) isozymes further oxidize acetaldehyde to acetate. In the metabolism of acetaldehyde, ALDH2 is the most active ALDH isozyme, followed by ALDH1B1 and ALDH1A1 (41, 42). Outside of the liver, the majority of the acetate produced is subsequently transformed into acetyl coenzyme A (CoA). NAD+ is reduced to NADH as a result of the ethanol oxidation process by the ADH and ALDH enzymes, lowering the NAD+/NADH ratio. Consequently, NAD+ availability is restricted. Additionally, NAD+ is a crucial cofactor needed for continuous ethanol oxidation. as well as to maintain vital metabolic processes like fatty acid oxidation, glycolysis, and the TCA cycle. Thus, in order to produce NAD+ and speed up the metabolism of alcohol, NADH must be reoxidized in the mitochondria by the electron transport chain (43).

Moreover, acetaldehyde, acetate, and alcohol-metabolizing enzymes are thought to be the ethanol metabolites' mechanisms in alcohol-induced CRC. The carcinogen acetaldehyde is well-known. It can weaken 1CM and produce ROS and RNS, both of which damage DNA. Moreover, it results in dysbiosis and elevated intestinal permeability, which trigger immunological dysfunction, inflammation, and cancer. While ethanol-inducible CYP2E1 and

ALDH1B1 affect Wnt/β-catenin signaling and procarcinogen production, respectively, genetic polymorphisms in ethanol-metabolizing enzymes like ALDH2 can alter the production of acetaldehyde. Acetate's metabolism to acetyl-CoA has more recently led to its association with CRC. One significant metabolite in cancer is acetyl-CoA (44).

Excessive alcohol intake may interact with other risk factors for CRC, such as smoking and certain dietary factors. The combined effect of these factors may further elevate the risk (45). It's worth noting that some studies suggest a potential protective effect of moderate alcohol consumption, particularly with red wine, due to the presence of certain compounds like resveratrol (46, 47). However, the overall consensus is that the potential risks of excessive alcohol intake outweigh any potential benefits. Many health organizations, including the World Health Organization and the American Cancer Society, recommend limiting alcohol intake to reduce the risk of various cancers, including CRC (46, 47).

3.1.3. Obesity

There is a well-established association between obesity and an increased risk of CRC. Numerous studies have consistently demonstrated a link between excess body weight, particularly abdominal or visceral obesity, and the development of CRC. Obesity, defined by a high body mass index (BMI), is associated with an elevated risk of developing colorectal cancer. This risk is particularly pronounced for cancers located in the colon (48).

Moreover, Central or abdominal obesity, characterized by excess fat around the waist, seems to have a stronger association with CRC than overall obesity (49). The accumulation of fat in the abdominal area is thought to be metabolically active and may contribute to inflammation and insulin resistance, which are factors linked to cancer development (50). Obesity is believed to influence CRC development through various mechanisms. Adipose (fat) tissue produces hormones and cytokines that can affect inflammation, insulin sensitivity, and cell proliferation, all of which are relevant to cancer development (51).

Furthermore, Obesity is often associated with insulin resistance and elevated insulin levels (hyperinsulinemia). Insulin and insulin-like growth factors may promote the growth of cancer cells. High insulin levels can also lead to increased production of insulin-like growth factor 1 (IGF-1), which is associated with cell growth and division (52, 53). Obesity is characterized by

a state of chronic low-grade inflammation. Inflammatory factors produced by adipose tissue, such as cytokines and adipokines, may contribute to the development and progression of CRC (54, 55). The association between obesity and CRC risk exists in both men and women. However, some studies suggest that the association may be stronger in men (56). The relationship between obesity and CRC highlights the importance of lifestyle factors in cancer prevention. Maintaining a healthy weight through a balanced diet and regular physical activity is considered a modifiable risk factor.

3.1.4. Type 2 diabetes

There is evidence to suggest an association between type 2 diabetes and an increased risk of CRC (57). Several studies have explored the relationship between these two conditions, and while the exact mechanisms are not fully understood, there are several factors that may contribute to the connection. Type 2 diabetes is characterized by insulin resistance, where the body's cells become less responsive to insulin. This can lead to elevated levels of insulin in the blood.

In addition to, Insulin and insulin-like growth factors (IGFs) may promote cell growth and division, and high levels of these hormones have been implicated in the development of certain cancers, including CRC (52, 53). Type 2 diabetes is often associated with chronic low-grade inflammation. Inflammation can create an environment that promotes cancer development. In colorectal cancer, inflammation may contribute to the initiation and progression of tumors (58). Elevated blood sugar levels (hyperglycemia) are characteristic of diabetes. High glucose levels may contribute to cancer development through various mechanisms, including increased oxidative stress and inflammation (59, 60). Type 2 diabetes and CRC share certain risk factors, such as age, a sedentary lifestyle, and a diet high in processed foods and low in fiber. These common risk factors may contribute to the observed association. Some medications used to manage type 2 diabetes, such as certain insulin analogs and insulin-like growth factor receptor (IGF-1R) inhibitors such as erlotinib, have been studied for their potential impact on cancer risk and progression (61-63).

3.1.5. Colonic microbiota

Fusobacterium nucleatum and Bacteroides fragilis are two types of bacteria that have been implicated in associations with CRC (64).

3.1.5.1. Fusobacterium nucleatum:

Fusobacterium nucleatum is a type of bacteria that is commonly found in the oral cavity, but it has been detected in colorectal tumors, and its presence has been associated with CRC (65-67). Research suggests that *Fusobacterium nucleatum* may play a role in promoting inflammation and interfering with the immune response in the colorectal environment, which could contribute to the development and progression of CRC. *Fusobacterium nucleatum* stimulates MYD88's Toll-like receptor 4 signaling, which in turn triggers nuclear factor-κB activation and enhanced expression of miR21, a miRNA that lowers RAS GTPase RASA1 levels. Patients showed a higher risk of unfavorable outcomes when they had both high levels of tissue *Fusobacterium nucleatum* DNA and miR21 (68). Some studies have suggested that a higher abundance of Fusobacterium nucleatum in colorectal tumors may be associated with poorer prognosis in CRC patients (69).

3.1.5.2. Bacteroides fragilis:

Bacteroides fragilis is a common component of the human gut microbiota. In some studies, a specific toxin-producing strain of *Bacteroides fragilis* (known as enterotoxigenic *Bacteroides fragilis* or ETBF) has been associated with an increased risk of CRC (70, 71). ETBF produces a toxin called Bacteroides fragilis toxin (BFT), which may contribute to the development of colorectal cancer by promoting inflammation and cellular changes in the colon (72). *Bacteroides fragilis*, including the toxin-producing strain, has been studied in the context of inflammatory bowel diseases (IBD) such as Crohn's disease and ulcerative colitis, which are known risk factors for CRC (73, 74).

3.2. Modifiable Nutritional lifestyle factors:

3.2.1. Red and Processed meat intake

There is substantial evidence suggesting a link between the consumption of red and processed meats and an increased risk of CRC (75). Red meat includes beef, pork, lamb, and veal, while processed meats are those that have undergone preservation methods, such as smoking, curing, or salting. Cooking red meat at high temperatures or processing meat can lead to the formation of certain carcinogenic compounds, such as heterocyclic amines (HCAs) and polycyclic aromatic hydrocarbons (PAHs). These compounds have been linked to an increased

risk of cancer (76-78). Red meat, particularly beef and lamb, contains heme iron. Excessive intake of heme iron may contribute to the production of harmful substances in the colon, which could promote the development of CRC (79, 80). Processed meats often contain additives like nitrates and nitrites, which can be converted into nitrosamines (81). Nitrosamines are known carcinogens and may play a role in the development of CRC (82, 83) The consumption of red and processed meats has been associated with increased markers of inflammation, and chronic inflammation is considered a risk factor for the development of various cancers, including CRC (84, 85).

Some red and processed meats are high in saturated fats, which may also contribute to an increased risk of CRC. High-fat diets have been associated with inflammation and oxidative stress (86). Numerous studies, including meta-analyses and systematic reviews, have consistently shown a positive association between a high intake of red and processed meats and an elevated risk of CRC. The International Agency for Research on Cancer (IARC) classifies processed meat as Group 1, meaning there is sufficient evidence to conclude that it is carcinogenic to humans (87). There appears to be a dose-response relationship, meaning that a higher intake of red and processed meats is associated with a higher risk of CRC (88, 89). Based on the evidence, many health organizations, including the World Health Organization and the American Cancer Society, provide recommendations to limit the consumption of red and processed meats for cancer prevention. They suggest opting for lean proteins, such as poultry, fish, and plant-based protein sources.

3.2.2. Low Vitamin D Level

There is evidence suggesting an association between low vitamin D levels and an increased risk of CRC. Vitamin D is a fat-soluble vitamin that plays a crucial role in various physiological processes, including maintaining bone health, supporting the immune system, and potentially influencing the risk of certain cancers. Numerous observational studies have explored the link between vitamin D status and CRC risk. These studies often measure circulating levels of 25-hydroxyvitamin D [25(OH)D], which is the main indicator of vitamin D status in the body (90, 91). There is evidence of geographic variation in CRC incidence, with higher rates observed in regions with less sunlight exposure. Sunlight is a primary source of vitamin D synthesis in the skin, and lower sunlight exposure can lead to reduced vitamin D levels (92, 93).

Moreover, Vitamin D may influence CRC risk through several mechanisms. It has anti-inflammatory properties, supports cell differentiation, and can regulate the cell cycle (94). Vitamin D receptors are present in colon cells, and the active form of vitamin D (calcitriol) can exert anticancer effects (95, 96). Some studies have reported an inverse association between higher vitamin D levels and a reduced risk of CRC (97). However, the strength and consistency of this association may vary across studies. Adequate vitamin D levels may have a protective effect against the development and progression of colorectal tumors. This has led to investigations into the potential use of vitamin D supplementation for CRC prevention.

3.2.3. Low fiber intake

There is evidence suggesting that low fiber intake is associated with an increased risk of CRC. Fiber is a component of plant-based foods that is not fully digested in the human digestive system. It includes both soluble and insoluble fibers, and it is found in fruits, vegetables, whole grains, legumes, and nuts (98). Numerous epidemiological studies have investigated the association between dietary fiber intake and CRC risk. These studies often compare the incidence of CRC in populations with varying levels of fiber consumption (99). Higher dietary fiber intake has been associated with a reduced risk of CRC. Fiber may have a protective effect through several mechanisms, including promoting regular bowel movements, diluting and binding carcinogens, and influencing the composition of the gut microbiota (100, 101).

Furthermore, improved colorectal health is associated with an adequate intake of fiber. By giving stool more volume and facilitating its passage through the colon more quickly, insoluble fiber shortens the amount of time that potentially hazardous materials come into contact with the intestinal lining (102). Short-chain fatty acids (SCFAs) are produced when bacteria in the colon ferment certain dietary fibers. SCFAs may help to maintain a healthy colon environment and may have anti-inflammatory properties (103, 104). Adenomas are precancerous polyps in the colon that can develop into CRC. Some studies suggest that higher fiber intake is associated with a reduced risk of colorectal adenomas (105). Public health recommendations often include a diet rich in fiber for overall health, including colorectal health. For adults, the general recommendation is to consume a variety of fiber-containing foods, aiming for at least 25 grams per day for women and 38 grams per day for men.

3.2.4. High Fat Diet

Research points to a possible link between a high-fat diet especially one heavy in saturated fats and a higher risk of CRC. Several epidemiological studies and scientific inquiries have examined the connection between dietary fat consumption and the risk of CRC. While the findings of observational studies have been inconsistent, there appears to be a correlation between a high intake of fat in the diet and a higher risk of CRC. The evidence supporting the consumption of processed and red meats, which are sources of saturated fats, is especially strong (106). A higher risk of CRC has been associated with diets heavy in saturated fats, which are frequently found in red meat and full-fat dairy products. Saturated fats may be involved in oxidative stress and inflammation, two processes linked to the development of cancer (107). High cooking temperatures, especially when grilling or frying meat, can release carcinogenic chemicals, such as heterocyclic amines (HCAs) and polycyclic aromatic hydrocarbons (PAHs). When ingested, these substances may increase the risk of CRC (108, 109).

Moreover, diets high in fat, particularly certain types of fat, may aggravate chronic inflammation. One known risk factor for the onset and spread of CRC is persistent inflammation. Certain fatty fish, such as those high in omega-3 fatty acids, may protect against colorectal cancer, according to some studies (110). Nonetheless, it's important to have a diet that balances the various forms of fats. Dietary fat and the risk of colorectal cancer may interact with other lifestyle factors like drinking alcohol, exercising, and following a general diet. The American Cancer Society and the World Health Organization are two health organizations that advise embracing a diet high in fruits and vegetables and low in processed and red meats and moderate in total fat intake to reduce the risk of CRC (108, 109).

Furthermore, regarding the potential mechanisms through which dietary fat contributes to CRC, recent studies have reported that fat-mediated alterations of the gut microbiota link bile acid metabolism to CRC risk and colonic tumorigenesis, exemplifying how gut microbial co-metabolism affects colon health (111). Most interestingly, Clinical data suggest that omega-3 fatty acids have differential anti-CRC activity depending on several host factors (including pretreatment blood omega-3 fatty acids level, ethnicity, and systemic inflammatory response) and tumor characteristics (including location in the colorectum, histological phenotype (eg, conventional adenoma or serrated polyp) and molecular features (eg, microsatellite instability,

cyclooxygenase expression)). Recent data also highlight the need for further investigation of the effect of omega-3 fatty acids on the gut microbiota as a possible anti-CRC mechanism, when used either alone or in combination with other anti-CRC therapies (112).

4. Conclusion

The risk of CRC is increased by a number of environmental lifestyle factors that are largely modifiable, including smoking, drinking too much alcohol, gaining weight, and. While obesity and physical inactivity are two risk factors that are common to both type 2 diabetes and CRC, people with type 2 diabetes still have an elevated risk even after adjusting for these variables. According to research on colonic microbiota, some bacterial species, like *Bacteroides fragilis* and *Fusobacterium nucleatum*, may increase the risk of CRC. More interestingly, there are some modifiable nutritional risk factors such as consuming red and processed meat, low fiber intake, low vitamin D Level, and consuming high-fat diet, which may increase the risk of CRC. (Summarized in Table 1). In this review, we focus on modifiable environmental lifestyle factors and nutritional factors to provide evidence for the significance of these factors on CRC incidence.

Table 1: Summary of modifiable environmental and nutritional lifestyle factors that have been associated with an increased risk of colorectal cancer (CRC).

Lifestyle Factor	Description	Ref.
High Red and Processed Meat	Increased consumption is associated with higher risk.	(27, 75)
Low Fiber Intake	Inadequate fiber intake may contribute to risk.	(98, 99)
High Saturated Fat	Diets high in saturated fats may increase the risk.	(106, 107)
Low Vitamin D Levels	Inadequate vitamin D levels have been associated with higher risk.	(90, 91)
Obesity	Excess body weight, particularly abdominal obesity, is a risk factor	(26, 48, 49)

Smoking	Tobacco smoking is associated with an increased risk.	(24, 31, 32)
Alcohol Consumption	Heavy alcohol consumption has been linked to higher risk.	(24, 40)
Type 2 Diabetes	Poorly managed diabetes may contribute to colorectal cancer risk.	(28, 57)
Colonic Microbiota	Fusobacterium nucleatum and Bacteroides fragilis are two types of bacteria that have been implicated in associations with colorectal cancer	(29, 30, 64)

Conflict of Interest

The authors declare no conflicting interest.

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