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Environmental factors, gut microbiota, and colorectal cancer prevention

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Abstract

The substantial burden of colorectal cancer and increasing trend in young adults highlight the importance of lifestyle modification as a complement to screening for colorectal cancer prevention. Several dietary and lifestyle factors have been implicated in the development of colorectal cancer, possibly through the intricate metabolic and inflammatory mechanisms. Likewise, as a key metabolic and immune regulator, the gut microbiota has been recognized to play an important role in colorectal tumorigenesis. Increasing data support that environmental factors are crucial determinants for the gut microbial composition and function, whose alterations induce changes in the host gene expression, metabolic regulation, and local and systemic immune response, thereby influencing cancer development. Here, we review the epidemiologic and mechanistic evidence regarding the links between diet and lifestyle and the gut microbiota in the development of colorectal cancer. We focus on factors for which substantial data support their importance for colorectal cancer and their potential role in the gut microbiota, including overweight and obesity, physical activity, dietary patterns, fiber, red and processed meat, marine

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Conflict of interest

Andrew T. Chan previously served as a consultant for Bayer Pharma AG, Pfizer Inc., Janssen, for work unrelated to the topic of this manuscript. This study was not funded by Bayer Pharma AG, or Pfizer Inc. No other conflict of interest exists.

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omega-3 fatty acid, alcohol, and smoking. We also briefly describe other colorectal cancer-preventive factors for which the links with the gut microbiota have been suggested but remain to be mechanistically characterized, including vitamin D status, dairy consumption, and metformin use. Given limitations in available evidence, we highlight the need for further investigations in the relationship between environmental factors, gut microbiota, and colorectal cancer, which may lead to development and clinical translation of potential microbiota-based strategies for cancer prevention.

Over the past three decades, the incidence rate of colorectal cancer has dropped by almost 45% in the United States, from a peak of 66.3 in 1985 to 37.5 per 100,000 persons in 2013. This is mirrored by a similar decline for colorectal cancer mortality, dropping from its peak of 28.6 in 1976 to 14.1 per 100,000 in 2014.¹ These trends are believed to be mainly attributable to increases in screening uptake (mainly colonoscopy) and reductions in certain risk factors (e.g., smoking and red meat consumption), with additional contributions from advances in treatment.² Despite these advances, colorectal cancer remains the third most common cancer and the third leading cause of cancer death in each sex in the country.¹ In 2018, an estimated total of 140,250 men and women will be diagnosed with colorectal cancer; 50,630 deaths will be attributable to the disease. A particularly alarming trend is the rising incidence of colorectal cancer in adults younger than 50 years old whose incidence has risen by 1.6% and mortality by 13% from 2000 to 2013–14.³ This increase has motivated the American Cancer Society to revise their recommended age to initiate colorectal cancer screening from 45 to 50 years old.⁴ Although the reasons for the increasing incidence of young-onset colorectal cancer have yet to be elucidated, the obesity epidemic and related changes in lifestyle patterns are thought to have played an important role. Therefore, the continued burden of colorectal cancer, particularly among young adults, highlight the critical need to consider novel prevention strategies beyond screening.

A variety of diet and lifestyle factors have been implicated in the development of colorectal cancer. Studies have consistently estimated that approximately 50–60% of incident colorectal cancer cases in the US can be prevented by lifestyle modification.^{5,6} Smoking, body fatness, alcohol drinks, and red and processed meat have been established to increase the risk of colorectal cancer, whereas physical activity and intake of dietary fiber, whole grains, dairy products, calcium supplements, vitamin D, and marine omega-3 fatty acid may lower disease risk.⁷ Furthermore, increasing data indicate a potential chemopreventive effect of metformin, an antidiabetic drug, for colorectal cancer.⁸

While the exact mechanisms through which each of these factors may affect colorectal cancer are likely to differ and largely remain to be elucidated, several lines of evidence suggest that the gut microbiome may represent a congregate mode of action mediating the relationship of environmental factors with colorectal cancer (Figure 1). First, the large intestine represents a vast microbial ecosystem, housing several trillion microbes that encode 100-fold greater unique genes than our own genome. The composition and function of this ecosystem appear to be largely shaped by environmental factors, particularly diet and lifestyle.⁹ Second, the gut microbiota plays an important role in nutrient processing and synthesis, and may affect colorectal cancer development through metabolite-mediated

changes in the immune and metabolic signals.¹⁰ Finally, increasing data indicate that gut microbes are pivotal in integrating environmental cues with host physiology and metabolism, and may influence several biological processes critical to carcinogenesis, including the balance of intestinal cell proliferation and death, systemic and local immune homeostasis, and alterations of the host metabolic activities.¹¹ Specifically for colorectal cancer, several microbes have been found to be differentially enriched in tumor versus normal tissues from the same host, or in fecal samples from patients with colorectal neoplasia versus healthy controls. Although the epidemiologic evidence remains limited and inconsistent, relatively consistent data indicate that *Fusobacterium nucleatum* (*F. nucleatum*) and *Bacteroides fragilis* are enriched in colorectal cancer, whereas butyrate-producing bacteria are depleted in cancer patients. The role of these and other microbes in colorectal cancer has been extensively reviewed elsewhere.^{12,13}

Herein, we review the evidence on how diet and lifestyle factors may influence colorectal cancer through gut microbiota-related mechanisms. We focus on factors for which substantial data support their importance for colorectal cancer and their potential role in the gut microbiota, including overweight and obesity, physical activity, dietary patterns, fiber, red and processed meat, marine omega-3 fatty acids, alcohol, and smoking. We also briefly describe other colorectal cancer-preventive factors for which the links with the gut microbiota have been suggested but remain to be mechanistically characterized, including vitamin D, dairy products, and metformin. For each factor, we review the epidemiologic evidence supporting its relationship with colorectal cancer and then summarize major findings about the interaction with the gut microbiota.

Overweight and obesity

Fueled by Western dietary patterns and sedentary lifestyle, the prevalence of obesity in US adults has almost tripled in the past few decades, rising from 13.4% in 1960–1962 to 37.7% in 2013–2014.^{14,15} Numerous epidemiologic studies have consistently associated higher body fatness in adulthood to increased risk of colorectal cancer (Table 1). Excess body weight has been estimated to contribute to approximately 5% of incident colorectal cancer cases in the US.⁵

Several metabolic and inflammatory factors, including insulin / insulin-like growth factor 1 signaling, sex hormones, adipokines, and systemic inflammation, have been proposed to underlie the relationship between obesity and colorectal cancer. On the other hand, the gut microbiota has emerged as an integral factor that modulates host metabolism and has been suggested to play a vital role in obesity-related metabolic alterations, including inflammation and insulin resistance.¹⁶ The complex, bidirectional relationship between obesity and the gut microbiota is indicated by the substantial changes in the gut microbial community induced by obesity and weight loss in animal and human studies, and recapitulation of obesity and its phenotypic features by fecal transplantation in gnotobiotic (germ-free) mouse models, as well as the positive association of antibiotic exposure in early life with childhood obesity.

Although obesity-induced changes in the gut microbiota may promote cancer development through modulation of microbe-derived proinflammatory molecules (e.g., lipopolysaccharide [LPS]) and metabolites (e.g., increased acetate and reduced butyrate) that impair gut barrier function and increase permeability,¹⁷ only recently has direct evidence emerged for the mechanisms through which the gut microbiota may mediate the relationship between obesity and cancer (Figure 2). Studies led by Wade and colleagues uncover a potential role of epigenetic alterations in the link between obesity, gut microbiota, and colorectal cancer.^{18–20} They showed that high-fat diet-induced obesity led to widespread remodeling of the acetylation landscape at presumptive *cis*-regulatory regions that likely influence the transcriptional responses integral to the initiation and progression of colon cancer.¹⁹ This epigenetic remodeling was found to be dependent on the gut microbiota as animals fed the same diet that received bacteria from non-obese donors did not show similar changes.²⁰ Gene expression analysis indicated that the combination of high-fat diet and fecal transplantation induced a gene expression profile that had partial resemblance to that observed in human colorectal cancer.¹⁹ These findings highlight potential interactions between obesity and microbiome and their effects on the host epigenome, which prime putative enhancers in the host colon epithelium for malignant transformation. In addition to modifications of the enhancer landscape, obesity may also promote colorectal cancer through changes in DNA methylation,¹⁸ although the role of the gut microbiota in this process remains to be elucidated. Interestingly, the consequences of obesity-associated epigenetic changes may be different according to age; in young mice, obesity was associated with a colonic cellular switch favoring long-chain fatty acid oxidation that may increase the number of intestinal stem/stem-like cells; whereas in aged mice, obesity was associated with decreased expression of tumor suppressor genes and negative feedback regulators of pro-survival and pro-proliferation pathways that in turn prime for unrestrained signaling to accelerate the initiation and progression of colon tumorigenesis once oncogenic events occur.¹⁸ These findings may have implications for explaining the role of the obesity epidemic in the recent increase in the incidence of young-onset colorectal cancer.

In addition to epigenetic mechanisms, changes in the gut microbial metabolites and constituents have also been implicated in the obesity-cancer link. Specifically, obesity enhances production of deoxycholic acid, a secondary bile acid that is produced solely by Gram-positive gut bacteria and known to cause DNA damage through reactive oxygen species production. Increased enterohepatic circulation of deoxycholic acid may promote hepatocellular carcinoma development by inducing cellular senescence and the senescence-associated secretory phenotype in hepatic stellate cells in the tumor microenvironment.^{21, 22} More recent evidence indicates that this effect requires cooperative induction of another Gram-positive gut microbial component, lipoteichoic acid, which upregulates the expression of prostaglandin-endoperoxide synthase 2 [also known as cyclooxygenase-2 (COX-2)] in deoxycholic acid-induced senescent hepatic stellate cells to promote cancer development in obese mice.²³ As a critical enzyme in inflammation, prostaglandin-endoperoxide synthase 2 mediates production of prostaglandin E₂ that suppresses antitumor immunity.²³ Given the potential role of prostaglandin E₂ and secondary bile acid in promoting colorectal cancer, further studies are needed to investigate whether microbial imbalance-induced metabolic change also mediates obesity-related tumor promotion in the colon.

Physical activity

Convincing evidence indicates that total and recreational physical activity reduces risk of colon cancer, whereas no benefit is found for rectal cancer. Recent animal evidence suggests that voluntary exercise can alter the composition of the gut microbiota and increase production of short-chain fatty acids (SCFAs).^{24–27} Exercise restored bacterial diversity in obese rats²⁶ and increased the ratio of *Bacteroidetes* to *Firmicutes*, which was reduced in obesity in a manner that was proportional to the intensity of exercise in mice.²⁵ Exercise also increased the relative proportion of butyrate-producing bacteria and the intestinal concentration of butyrate (Table 1).^{24, 25} However, whether these effects can be generalized to human remains largely unknown. A study compared the gut microbiome between 40 male elite professional rugby players and two control groups; one matched for athlete size with a comparable body mass index (n=23) and another reflecting the background age- and gender-matched population (n=23). It found that the athletes had a more diverse gut microbiota than either of the control groups and the increased gut microbiota diversity in athletes was driven by substantially higher exercise and protein intake.²⁸ When the metabolic profile and functional capacity of the gut microbiota were examined, compared to control groups, athletes had relative increase in pathways related to amino acid and antibiotic biosynthesis, and carbohydrate metabolism, as well as increased levels of fecal metabolites (e.g., SCFAs) associated with enhanced muscle turnover and overall health.²⁹

Dietary patterns

The hypothesis that a Western dietary pattern increases colorectal cancer risk originates from the observation that Japanese migrants to Hawaii acquire the same risk of colorectal cancer as that experienced by Caucasians in the US. This hypothesis is supported by subsequent epidemiologic studies in different countries showing an increased risk of colorectal cancer among individuals consuming a Western-style diet that is high in red and processed meats, refined grains, soda, and sweets, and low in fruits, vegetables and whole-grain products (Table 1).³⁰ In contrast, a lower risk of colorectal cancer has been observed in individuals adhering to a prudent diet that is high in fruits, vegetables, whole grains, fish, soy, poultry, and low-fat dairy.³⁰

A potential role of the gut microbiota in mediating the associations of dietary patterns with colorectal cancer risk is supported by the dramatic difference in the gut microbial structures and metabolite profiles between populations consuming different diets. The gut microbiota of rural Africans, whose diet is rich in fiber and low in fat, is characterized by a predominance of *Prevotella* genus that is involved in starch, hemicellulose, and xylan degradation, whereas the American microbiota is predominated by *Bacteroides* genus with a higher abundance of potentially pathogenic proteobacteria, such as *Escherichia* and *Acinetobacter*.³¹ These microbial structural differences parallel the lower colorectal cancer rates in Africa than Western countries. Similar differences exist in the profile of fecal metabolites, with SCFAs higher in native Africans and secondary bile acids higher in African Americans. These observational findings have been supported by an interventional study demonstrating that switching African Americans to a high-fiber, low-fat diet for 2 weeks increases production of SCFAs, suppresses secondary bile acid synthesis, and reduces

colonic mucosal inflammation and proliferation biomarkers of cancer risk.³² In contrast to the pro-cancer effect of secondary bile acids, SCFAs have been shown to protect against colorectal cancer by their beneficial effects on the immune and metabolic pathways, as detailed below in the section for Fiber.

Recent mechanistic studies suggest that impairment of the colonic mucus layer, a physical barrier that separates trillions of gut bacteria from the host, may represent a potential mechanism through which a Western diet may interact with the gut microbiota to promote carcinogenesis.^{33, 34} A Western diet slows mucus growth rate and increases penetrability of the colonic mucus barrier, and this effect co-occurs with the shifts in microbial community characterized by gradual decrease of SCFA-producing bacteria, such as *Bifidobacterium* and *Bacteroidales* family S24–7, and increases in *Firmicutes*.³³ Transplantation of the microbiota from chow-fed mice to Western-diet-fed mice restored the gut microbial structure and the growth and penetrability of the inner colonic mucus.

For prudent diet, we recently reported that its beneficial association with colorectal cancer was much stronger for tumors enriched with *F. nucleatum*.³⁵ *F. nucleatum* is the most studied bacteria for colorectal cancer and clinical data have consistently implicated *F. nucleatum* in colorectal cancer.^{36–45} High abundance of *F. nucleatum* in tumor tissue has also been associated with poor survival in patients with established colorectal cancer.^{45, 46} Experimental evidence supports that *F. nucleatum* may promote colorectal cancer development and progression by activating the β -catenin pathway and potentiating tumoral immune evasion through recruitment of immunosuppressive myeloid cells and inhibition of natural killer cell function.^{47–49} Higher abundance of *F. nucleatum* in colorectal cancer tissue has been associated with lower density of tumor-infiltrating CD3+ T cells,⁵⁰ supporting a role of *F. nucleatum* in attenuating antitumor immunity. Given the immunomodulatory benefits of some dietary factors (e.g., fiber and marine omega-3 fatty acid), it is possible that a healthy dietary pattern may diminish the carcinogenic effects of *F. nucleatum* by restoring effective immunosurveillance against malignant transformation and distant migration. Indeed, a recent dietary cross-over study observed a marked increase in stool *F. nucleatum* levels after rural Africans were switched to a low-fiber, high-fat diet and a decrease in *F. nucleatum* among African Americans who changed to a high-fiber, low-fat diet.³²

Fiber

Despite the longstanding hypothesis that a high-fiber diet may protect against colorectal cancer by minimizing exposure to intestinal carcinogens, epidemiologic studies associating dietary fiber intake with subsequent risk of colorectal cancer have yielded inconsistent results.⁵¹ This inconsistency may be related to several factors, including variable degree of confounding control across studies (those with more rigorous adjustment for other dietary factors tend to report null results), large variations in fiber consumption across populations (a threshold effect has been reported in some studies for fiber intake in relation to colorectal cancer), variation in dietary sources of fiber (compared to other sources, cereal fiber has been more strongly and consistently associated with lower risk of colorectal cancer), and heterogeneity across tumor subtypes.⁵¹ Similarly, randomized clinical trials (RCTs) testing

fiber supplementation among patients with a history of colorectal polyps also reported inconsistent findings.^{52–57} These inconsistencies may be related to the variation in the compliance and duration of the intervention and length of follow-up period.⁵¹ Nonetheless, based on existing evidence, the most recent expert report from the World Cancer Research Fund and American Institute for Cancer Research in 2017 concludes that there is probable evidence that consumption of foods containing dietary fiber protects against colorectal cancer (Table 1).⁷

Fiber is the major substrate of gut bacterial fermentation that produces a family of beneficial metabolites, the so-called SCFAs, which include butyrate, acetate, and propionate (Figure 3). Some,⁵⁸ but not all,⁵⁹ studies have shown that higher fiber intake enriches *Lactobacillus* spp. and butyrate-producing bacteria in the gut, such as *Bifidobacterium*, *Clostridium*, *Anaerostipes*, *Eubacterium*, and *Roseburia* species, and increases production of SCFAs. Laboratory data support the benefit of SCFAs for colorectal cancer. Studies using gnotobiotic mouse models have provided compelling evidence that dietary fiber protects against colorectal tumorigenesis in a microbiota- and butyrate-dependent manner via inhibition of histone deacetylase.⁶⁰ The combination of high-fiber diet and butyrate-producing bacterium *Butyrivibrio fibrisolvens* reduced colorectal tumor incidence and multiplicity, whereas neither *B. fibrisolvens* nor high fiber had a protective effect on their own. Therefore, the between-individual variation in the gut microbiota may be another potential explanation for the inconsistency in epidemiologic findings relating fiber intake to colorectal cancer risk. Indeed, we recently showed that both whole grains and a prudent diet that is high in fiber were associated with lower risk of colorectal tumors that had detectable *F. nucleatum*, whereas no association was found for tumors without *F. nucleatum*.³⁵ Future studies are warranted to test whether the variation in SCFA-producing bacteria may also modify the relationship between fiber intake and colorectal cancer risk.

In addition to epigenetic regulation, increasing data support the crucial role of butyrate and other SCFAs in intestinal immune homeostasis through modulation of regulatory T cells (Tregs).⁶¹ Tregs play a central role in suppression of inflammatory and allergic responses by limiting proliferation of effector CD4+ T cells. Butyrate and propionate have been shown to induce extrathymic generation and functional differentiation of Tregs and protect against colitis.^{61, 62} Possible mechanisms include inhibition of histone deacetylase, enhancement of anti-inflammatory phenotype in colonic macrophages and dendritic cells via activation of GPR109a, and a T-cell intrinsic epigenetic upregulation of the Foxp3 gene, a master regulator of Treg function.

While the role of Tregs in colorectal cancer remains controversial, partly due to its functional heterogeneity, higher levels of immune checkpoints and other immunosuppressive molecules expressed in Tregs and cancer cells has been implicated in immune evasion of tumors, adversely influencing prognosis.^{63–65} Antibodies targeting these immune checkpoints are the basis for immunotherapies which have revolutionized the treatment of many advanced malignancies, including colorectal cancer. Interestingly, patients with higher abundance of SCFA-producing bacteria, such as *Bifidobacterium*^{66, 67} and *Faecalibacterium*,⁶⁸ appear to be more responsive to immunotherapy, further supporting the importance of SCFA in modulation of tumor immunity. Moreover, higher intake of fiber and whole grains

after diagnosis has been associated with better survival of colorectal cancer.⁶⁹ Further studies are needed to evaluate whether this beneficial association is mediated by the gut microbiota and how patients' diet, including fiber intake, may shape and interact with their gut microbial community to influence the efficacy of immunotherapy and resistance to immune-related toxicity of immune checkpoint inhibitors in colorectal cancer.

Red and processed meat, bile acid and sulfur

Compelling data indicate that higher intake of red and processed meats is associated with increased risk of cancer, particularly colorectal cancer (Table 1).⁷⁰ Therefore, the International Agency for Research on Cancer has classified processed meat as a carcinogen to humans. Several elements in red and processed meats have been suggested to have pro-cancer effects, including preservatives (e.g., nitrates and nitrites), certain nutrients enriched in meats (e.g., heme iron, sulfur, and saturated fat), and chemicals produced during meat processing and cooking (e.g., heterocyclic amines and polycyclic aromatic hydrocarbons).

Recent evidence suggests a critical role of the gut microbiota in mediating the effect of carcinogenic factors in red meats (Figure 4). For example, the gut microbiota is required for the damaging effect of heme iron on the colonic surface epithelium. Heme iron elicited an eightfold increase in the abundance of mucin-degrading bacteria *Akkermansia muciniphila*, leading to disruption in the mucus barrier function. Antibiotics abolished heme-induced injuries as well as the downstream carcinogenic effects, including compensatory hyperproliferation, hyperplasia, and differential expression of tumor suppressors and oncogenes.⁷¹

In addition to the direct effect on the gut microbiota, compounds associated with high intake of red meat can serve as substrates for gut microbial metabolism and contribute to colorectal carcinogenesis. Two of the most studied compounds include secondary bile acids and sulfur. The high content of saturated fat in red and processed meats is associated with increased secretion of bile acids in the liver to emulsify dietary fat for absorption by the small intestine. Although the majority of bile acids are reabsorbed in the small intestine, those entering the colon are metabolized by the anaerobic bacteria (e.g., *Clostridium* clusters XIVa and XI and *Eubacterium*) into secondary bile acids, including lithocholic acid and deoxycholic acid. Secondary bile acids are potential mutagens and can induce DNA damage and apoptosis resistance by causing oxidative/nitrosative stress and liberating reactive oxygen/nitrogen species. In support of the potential role of secondary bile acids in colorectal cancer, a recent prospective cohort study found an elevated risk of proximal colon cancer among patients with ultrasound-detected gallstone disease and cholecystectomy.⁷² These patients are expected to have higher concentrations of fecal secondary bile acids due to a continuous bile flow into the bowel and increased activity of secondary bile acid-producing bacteria.^{73,74} The predominant association with proximal colon cancer may reflect a greater proximal colonic absorption of fecal secondary bile acids.⁷⁵

Moreover, recent evidence indicates a crosstalk between bile acids as signaling molecules and the gut microbiota for regulation of host metabolism.⁷⁶ Specifically, bile acids and gut bacteria interact with the nuclear farnesoid X receptor and the G protein-coupled membrane

receptor 5 (TGR5) to regulate numerous metabolic pathways that are potentially important for cancer development. In particular, TGR5 activation in colonic L cells increases synthesis and release of glucagon-like peptide-1 (GLP-1),⁷⁷ a metabolic hormone that enhances the secretion of insulin and controls glucose homeostasis. Interestingly, GLP-1 receptor agonists have been showed to promote intestinal growth and colonic tumorigenesis in mice,⁷⁸ and liraglutide, a GLP-1 receptor agonist approved for treatment of type 2 diabetes, has been associated with increased risk of several cancers, including colorectal cancer, although findings remain inconsistent.⁷⁹ These data additionally support a potential role of bile acids in cancer development through microbiota-dependent metabolic mechanisms.

Sulfur is another compound that is enriched in red and processed meat and can potentially influence colorectal carcinogenesis through microbial mechanisms.⁵¹ Inorganic sulfur (sulfate and sulfite) routinely used as a preservative in processed meat and sulfur contained in amino acids (e.g., cysteine and methionine) from red meat can be metabolized by sulfur-reducing bacteria to hydrogen sulfide, which has been implicated in inflammatory bowel disease and colorectal cancer.⁸⁰ Patients with colitis and colorectal cancer have higher levels of fecal hydrogen sulfide than disease-free controls.⁸¹ Excess production of hydrogen sulfide in the colon may promote carcinogenesis through multiple mechanisms, including DNA damage due to its genotoxic properties, impaired colonocyte nutrition by inhibition of β -oxidation of butyrate, reduced integrity of the mucus layer for bacterial degradation, induction of epithelial hyperproliferation, and increase in inflammation by altered immune cell populations and function.⁵¹ Consistent with these mechanistic data, a recent study found that the abundance of sulfur-reducing bacteria, such as *Bilophila wadsworthia* and *Pyramidobacter* spp., was higher in colonic mucosa of patients diagnosed with colorectal cancer, compared to cancer-free individuals undergoing routine screening colonoscopy.⁸² Interestingly, a particularly higher abundance of sulfur-reducing bacteria was found in African Americans than non-Hispanic whites, regardless of disease status, suggesting that increased production of hydrogen sulfide may predispose African Americans to a higher risk of colorectal cancer than non-Hispanic whites. The study also identified a positive correlation between abundance of sulfur-reducing bacteria and the components of a diet high in fat and animal protein, and a negative correlation with the consumption of dairy and calcium.⁸²

Marine omega-3 fatty acids

The anti-inflammatory activity of marine omega-3 fatty acids, including mainly eicosapentaenoic acid and docosahexaenoic acid, has been well recognized. Increasing data support a potential benefit of marine omega-3 fatty acids for colorectal cancer.⁸³ A recent meta-analysis of prospective cohort studies indicates that individuals with the highest level of marine omega-3 fatty acids in biospecimens had 24% lower risk of colorectal cancer than those with the lowest levels (Table 1),⁸⁴ although the findings on dietary intake remain inconsistent, possibly due to the long latency for any protective effect and heterogeneity across tumor subsites and subtypes.⁸⁵ In a RCT of patients with familial adenomatous polyposis, supplementation of eicosapentaenoic acid at a dose of 2 g daily for 6 months reduced the number and size of polyps by 20–30%, an effect comparable to cyclooxygenase-2 inhibitors.⁸⁶ In addition to protection against colorectal cancer incidence,

recent data support a survival-improving benefit of high marine omega-3 fatty acid intake among patients with established colorectal cancer.^{87–89} These data together support that marine omega-3 fatty acids may have a beneficial effect across the entire spectrum of colorectal cancer initiation, progression, and distant metastasis.

Dietary fat composition has been suggested as a major driver of the gut microbial community structure. Compared to other types of fat, omega-3 fatty acids have been associated with higher intestinal microbiota diversity and omega-3 fatty acids-rich diet ameliorates the gut dysbiosis induced by omega-6 polyunsaturated fatty acids or antibiotics. Data from mouse models suggest that dietary omega-3 fatty acid intake or high tissue levels of omega-3 fatty acids are associated with an increased abundance of anti-inflammatory bacteria, such as lactic acid-producing bacteria (mainly *Lactobacillus* and *Bifidobacterium*), and decreased abundance of immunosuppressive and pro-inflammatory bacteria, such as *F. nucleatum*, LPS-producing bacteria (e.g., *Escherichia coli*) and *Akkermansia* (Figure 5).^{90–96} A dietary intervention that included 600mg of omega-3 fatty acid daily for 14 days has been shown in a case report to significantly enrich several SCFA-producing bacteria, including *Roseburia*, *Blautia*, *Bacterioides*, and *Coproccoccus*.⁹⁷ Moreover, treatment of 2 g/ daily eicosapentaenoic acid for 90 days in 19 patients with long-standing ulcerative colitis has been shown to reduce mucosal inflammation, promote endoscopic and histological remission, and restore the gut microbial composition by increasing *porphyromonadaceae* and decreasing *Ruminococcaceae*.⁹⁸ In addition, a recent randomized cross-over trial in 22 middle-aged, healthy volunteers found that 8 weeks' treatment with 4 g mixed eicosapentaenoic acid/docosahexaenoic acid separated by a 12-week 'washout' period induced a reversible increase in several genera, including *Bifidobacterium*, *Roseburia* and *Lactobacillus*, although the overall α or β diversity did not significantly change.⁹⁹

Several potential pathways may contribute to the microbe-modifying effect of omega-3 fatty acids. A recent study showed that high omega-3 fatty acid might alter the production of microbiota regulators in colonic tissue.¹⁰⁰ Omega-3 fatty acid metabolite resolvin stimulates host epithelial expression of a transmissible factor, intestinal alkaline phosphatase,¹⁰¹ whose LPS-detoxifying activity leads to decreased abundance of LPS-producing and/or pro-inflammatory bacterial groups and increased abundance of LPS-suppressing and/or anti-inflammatory bacteria.¹⁰⁰ Moreover, luminal unabsorbed omega-3 fatty acids may alter the gut environmental conditions and omega-3 fatty acid-induced changes in the immune response may in turn confer selective pressure on the gut microbial community.

Mechanistically, the microbiota-modulating effect of omega-3 fatty acids may lead to improved immune function that prevents against colorectal cancer. Some species from *Lactobacillus* and *Bifidobacteria* genera, which have been consistently associated with marine omega-3 fatty acids, play an important role in the host immunoprotective system,^{102,103} promote antitumor immunity, and facilitate cancer immunotherapy.^{67, 104, 105} On the other hand, higher serum levels of LPS antibodies have been associated with increased CRC risk in men,¹⁰⁶ and higher abundance of *F. nucleatum* has been linked to higher risk and shorter survival of CRC.^{36–38, 41, 43,46} Interestingly, *Lactobacillus* and other anaerobic gut bacteria have been implicated in the saturation of polyunsaturated fatty acid, a detoxifying mechanism that transforms bacterial growth-inhibiting polyunsaturated fatty acid into less

toxic fatty acid, such as hydroxyl fatty acid.^{107–113} These microbial metabolites may help preserve intestinal barrier integrity, reduce oxidative stress, and lower inflammation.^{114, 115} Given that *Lactobacillus* is selectively enriched by omega-3 fatty acids, there may exist a reciprocal mechanism by which gut microbes adapt to host dietary change with functional consequences for host health. Moreover, a cross-feeding effect has been noted between human *Bifidobacterium*, which produces lactate and acetate, and the butyrate-producing species, such as *Eubacterium rectale*, which convert lactate to butyrate.^{116–118} Given the potential role of butyrate in epigenetic regulation and immune function, this may represent another mechanism by which omega-3 fatty acids protect against colorectal cancer (Figure 5).

Alcohol

Alcohol consumption has been associated with increased risk of colorectal cancer in a dose-dependent manner (Table 1). The positive association has been observed for wine, beer and spirits, and does not appear to differ by tumor subsite, sex or geographic region.⁷

Several, albeit preliminary, lines of evidence indicate a role of the gut microbiota in the tumorigenic effect of alcohol. First, both human and animal studies have shown that chronic ethanol consumption causes dysbiosis, lowers the abundances of *Bacteroidetes* and *Firmicutes*, and enriches *Proteobacteria* and *Actinobacteria*.^{119–121} These structural changes in the gut microbiota have been linked to intestinal bacterial overgrowth and hyperpermeability, leading to increased translocation of gram-negative microbial bacterial products (e.g., endotoxins) from the intestinal lumen into systemic circulation.^{120, 122} On the other hand, abstinence from alcohol has been shown to restore gut barrier integrity in humans.¹²³ Considering that endotoxemia has been implicated in the development of systemic inflammation, insulin resistance, and type 2 diabetes, these data suggest a link between alcohol consumption, gut microbiota, and increased metabolic risk associated with colorectal cancer. Moreover, chronic ethanol exposure has been shown to lower the abundance of butyrate-producing taxa from the *Clostridiales* order, including *Faecalibacterium prausnitzii*, *Coprococcus eutactus*, and *Roseburia* spp.¹²⁴ Through comprehensive characterization of the metabolic alterations of the content of the gastrointestinal tract, a study found that rats with ethanol exposure displayed significant changes in numerous metabolic pathways critical for host physiology, including a significant decrease in SCFAs.¹²⁵ Finally, in addition to colorectal mucosal cells, several intestinal aerobes and facultative anaerobes play important roles in the production of mutagen acetaldehyde from ethanol under aerobic conditions in the colon and rectum.¹²⁶ Several bacteria have been identified as potential acetaldehyde accumulators, including *Ruminococcus*, *Collinsella*, *Prevotella*, and *Coriobacterium*,¹²⁷ leading to the hypothesis that structural alterations of the gut microbiota in high alcohol consumers may increase oxidation of ethanol and intracolorectal levels of acetaldehyde above the minimum mutagenic concentrations to initiate carcinogenesis. Further mechanistic studies are needed to test this hypothesis.

Smoking

Smoking is associated with an increased risk of colorectal cancer with a prolonged latency period (Table 1). Compared to never smokers, former smokers remained at higher risk for up to about 25 years after quitting.¹²⁸ A population-based metagenomics analysis identified a modest negative correlation between smoking and the diversity of the gut microbiome.¹²⁹ A study using targeted fluorescent *in situ* hybridization identified higher *Bacteroides-Prevotella* in the fecal samples of smokers than non-smokers.¹³⁰ Conversely, smoking cessation has been shown to restore, at least partly, the diversity of the gut microbiome; increase the abundance of key representatives from the phyla of *Firmicutes* (*Clostridium coccoides*, *Eubacterium rectale*, and *Clostridium leptum* subgroup) and *Actinobacteria* (HGC bacteria and *Bifidobacteria*); and decrease the abundance of *Bacteroidetes* (*Prevotella* spp. and *Bacteroides* spp.) and Proteobacteria.¹³¹ The smoking-related microbial changes may lead to altered epithelial mucin composition of the mucus layer and increased inflammatory response.¹³² In addition, some *in vitro* and animal studies found that cigarette smoke might decrease the fecal abundance of *Bifidobacterium* and reduce its production of SCFAs.^{133, 134}

Although the causes of smoking-associated changes in the composition of the gut microbiota remain to be elucidated, preliminary evidence suggests a collective role of host, microbial, and environmental changes, such as intestinal and immune disruption, impaired clearance of pathogens, changes in the virulence of bacteria and fungi, altered growth and exopolysaccharide structure of known gut bacteria that may contribute to dysbiosis (e.g., *Bifidobacterium animalis*), and ingestion of bacteria that are present in cigarettes.¹³⁵

Others

Several other dietary and chemopreventive agents associated with colorectal cancer have been implicated in modulation of the composition and function of the gut microbiota (Table 1).

Predominant evidence from studies on dietary and supplementary vitamin D intake and circulating 25-hydroxyvitamin D levels indicates a beneficial effect of vitamin D on colorectal cancer incidence and mortality.^{136, 137} These data are consistent with the mechanistic evidence for a diversity of anti-cancer effects of vitamin D, particularly through its anti-inflammatory and immune regulatory properties.⁵¹ In support of the potential mediating role of the gut microbiota, a recent genome-wide host-microbiota association study identified variants in the vitamin D receptor gene among the most significant loci that were associated with overall gut microbial variation and abundance of individual bacteria, as well as functions of gastrointestinal and immune-related tissues and cells.¹³⁸

Moreover, there is strong evidence that higher intake of total dairy, milk and calcium is associated with lower risk of colorectal cancer.⁷ In addition to calcium and vitamin D, other constituents in dairy products have antineoplastic activity, including conjugated linoleic acid, lactose, butyrate, and lactic acid-producing bacteria.⁵¹ A recent intervention study of patients with irritable bowel syndrome showed that consumption of a fermented milk

product containing dairy starters and *Bifidobacterium animalis* potentiated colonic production of SCFAs and decreased abundance of *Bilophila wadsworthia*, a pathobiont that has been linked to inflammation and colorectal cancer, suggesting the influence on the gut microbial composition and function of the microbes and other compounds in dairy.¹³⁹

Finally, increasing data suggest the tumor-suppressive effect of metformin, a biguanide derivative that is widely used as the first-line treatment for type 2 diabetes.⁸ A recent small RCT found that 1-year administration of low-dose metformin in non-diabetic patients reduced the incidence and number of metachronous adenomas and polyps after polypectomy, providing further support for the potential of metformin in colorectal cancer chemoprevention.¹⁴⁰ Mechanistically, metformin has been shown to reduce cellular proliferative activity through activation of AMP-activated protein kinase,¹⁴¹ protect against immune evasion of tumors by countering the functional exhaustion of tumor infiltrating lymphocytes,¹⁴² and accumulate in colonic tissue in a considerable concentration (approximately 150-fold higher than in plasma).¹⁴³ In a recent RCT of 40 patients with type 2 diabetes, metformin altered the composition of gut microbiota by increasing the abundance of *Escherichia* and *Bifidobacterium* and decreasing the abundance of *Intestinibacter*, thereby increasing production of SCFAs.¹⁴⁴

Concluding remarks

Research has begun to elucidate the interplay between environmental factors and gut microbiota in carcinogenesis. However, direct evidence linking lifestyle and gut microbiota to colorectal cancer remains lacking, and the existing evidence on the relationship of lifestyle with gut microbiota has largely been based on small crosssectional or short-term intervention studies. Given the long latency of colorectal cancer development, high-quality prospective studies with lifestyle data collected over the life course and gut microbial composition and function assessed well prior to neoplastic occurrence are critically needed to elucidate how environmental factors may influence cancer risk through modulation of the gut microbiota. Moreover, further mechanistic studies using either gnotobiotic animal models or biomarker-based human trials are needed to complement the epidemiologic investigations and uncover pathways through which exogenous factors influence the carcinogenic process by interacting with the gut microbiota and host immune and metabolic systems. These collective efforts will hopefully lead to development and clinical translation of potential microbiota-based strategies for cancer prevention.

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Figure 1.

Framework for the interplay between diet and gut microbiota in colorectal cancer through influences on the host metabolism and immunity. Diet is a major determinant of the gut microbial community structure, whereas some bacteria in the gut are important for processing and synthesis of certain nutrients. The interaction between diet and gut microbiota may influence colorectal carcinogenesis through alterations in the host metabolism and immune system.

Figure 2.

Gut microbiota-related mechanisms through which obesity may increase risk of colorectal cancer. Obesity-induced changes in the gut microbiota lead to 1) increased levels of microbial-derived proinflammatory molecules that disrupt the gut barrier function; 2) epigenetic remodeling and modification of the gene expression in colonic epithelial cells; 3) alterations in the gut microbial metabolites that can cause DNA damage and dampen antitumor immunity. LPS, Lipopolysaccharides; PGE₂, Prostaglandin E₂.

Figure 3.

Potential benefits of short-chain fatty acids that may contribute to the anticancer effects of fiber. Short-chain fatty acids may epigenetically modulate expression of numerous cancer-related genes through inhibition of the activity of histone deacetylase, suppress inflammation by interaction with the G protein-coupled receptors (e.g., GPR43, GPR109a) at the colonic epithelial cell surface, and support intestinal immune homeostasis by modulation of the function of regulatory T cells.

Figure 4.

Potential role of the gut microbiota in mediating the effect of carcinogenic factors in red meats. Heme iron may damage the mucus barrier function by increasing the abundance of mucin-degrading bacteria (e.g., *Akkermansia muciniphila*). Increased production of secondary bile acids associated with high red meat consumption can promote carcinogenesis through increased oxidative stress and regulation of host metabolism. Excess production of hydrogen sulfide by sulfur-reducing bacteria in the colon may promote carcinogenesis through DNA damage, impaired colonocyte nutrition, reduced integrity of the mucus layer, induction of epithelial hyperproliferation, and increased inflammation.

Figure 5.

Pathways linking marine omega-3 fatty acid, gut microbiota, and immune function in colorectal cancer. Marine omega-3 fatty acid increases the abundance of *Bifidobacterium* and *Lactobacillus* genera and reduces the abundance of *Fusobacterium nucleatum* and lipopolysaccharide (LPS)-producing bacteria (e.g., *Escherichia coli*), possibly by altering the production of microbiota regulators (e.g., intestinal alkaline phosphatase [IAP]) via changes in tissue lipid mediators (e.g., resolvins) or by modifying the gut environmental conditions that in turn confer selective pressure on the microbial community. The changes in the microbial composition can, either directly or indirectly via microbial metabolites (e.g., hydroxyl fatty acids and short-chain fatty acids), help preserve intestinal immune homeostasis and protect against colorectal cancer, whereas some immune factors can

conversely affect the makeup of the microbiota, promoting a reciprocal host-microbe interaction.

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Table 1.

Summary of evidence and potential mechanisms underlying the relationship between environmental factors, gut microbiota, and colorectal cancer.

Risk factor	Estimated association with colorectal cancer [IRR (95% CI)]*	Associated microbes	Potential microbiota-related mechanisms
Overweight and obesity	1.05 (1.03–1.07) per 5 kg/m ² increase in body mass index	↓ <i>Bacteroidetes</i> : <i>Firmicutes</i> ratio	Increased LPS levels; epigenetic changes in the colonic epithelial cells; increased production of DNA-damaging bile acids
Physical activity	0.80 (0.72–0.88) comparing the highest to the lowest levels	↑ <i>Bacteroidetes</i> : <i>Firmicutes</i> ratio; ↑ SCFAs-producing bacteria	Increased production of SCFAs; changes in the metabolism of the microbiota.
Smoking	1.26 (1.11–1.43) for current smokers and 1.18 (1.09–1.27) for former smokers, compared to never smokers [†]	↓ Diversity ↑ <i>Firmicutes</i> , <i>Actinobacteria</i> , ↑ <i>Bacteroidetes</i> , <i>Proteobacteria</i>	Altered mucin composition of the mucus layer and increased inflammatory response.
Diet			
Western dietary pattern	1.40 (1.26–1.56) comparing the highest to the lowest category of the Western diet score [‡]	↑ <i>Bacteroides</i> , <i>Escherichia</i> , and <i>Acinetobacter</i> , ↑ <i>Prevotella</i>	Lower production of SCFAs from fiber deficiency
Fiber	0.93 (0.87–1.00) per 10 g/day increase in dietary consumption	↑ SCFAs-producing bacteria	Epigenetic regulation and immunomodulatory benefits of SCFAs
Red and processed meat	1.12 (1.04–1.21) per 100 g/day increase in consumption	↑ Mucin-degrading bacteria (e.g., <i>Akkermansia muciniphila</i>)	Microbiota-dependent barrier dysfunction induced by heme iron; Increased production of secondary bile acids and hydrogen sulfide by microbiota associated with high red meat consumption
Marine omega-3 fatty acid	0.76 (0.59–0.97) comparing the highest to the lowest category of biospecimen composition of marine omega-3 fatty acids [§]	↑ <i>Lactobacillus</i> and <i>Bifidobacterium</i> , ↓ <i>F. nucleatum</i> and LPS-producing bacteria	Preserved intestinal immune homeostasis due to increased abundance of immune-protective bacteria and reduced abundance of proinflammatory bacteria, as well as increased production of SCFAs and lipid mediators
Alcohol	1.07 (1.05–1.08) per 10 g/day increase in consumption	Dysbiosis; ↓ <i>Bacteroidetes</i> , <i>Firmicutes</i> , and butyrate-producing bacteria; ↑ <i>Proteobacteria</i> and <i>Actinobacteria</i>	Intestinal bacterial overgrowth and hyperpermeability; reduced production of SCFAs; bacterial production of acetaldehyde from ethanol
Dairy products	0.87 (0.83–0.90) per 400 g/day increase in consumption	↓ <i>Bifidobacteria wadsworthia</i>	Increased production of SCFAs and decreased abundance of proinflammatory pathogens
Vitamin D	0.92 (0.85–1.00) per 30 nmol/L increase in	Variants in the vitamin D receptor gene are among the most	Unclear

Risk factor	Estimated association with colorectal cancer [RR (95% CI)]*	Associated microbes	Potential microbiota-related mechanisms
	circulating vitamin D	significant loci associated with gut microbial composition	
Metformin	0.80 (0.64–1.00) comparing users to nonusers ^{//}	↑ <i>Escherichia</i> and <i>Bifidobacterium</i> ; ↓ <i>Intestinibacter</i>	Increased production of SCFAs.

Abbreviations: CI, confidence interval; LPS, lipopolysaccharides; RR, relative risk; SCFA, short-chain fatty acid.

* Data are derived from the meta-analysis conducted by the World Cancer Research Fund/American Institute for Cancer Research (reference 7), unless stated otherwise.

[†]Reference 128.

[‡]Reference 30.

[§]Reference 84.

^{//}Reference 8.