Current Colorectal Cancer Reports (2018) 14:251–265
https://doi.org/10.1007/s11888-018-0419-4

NUTRITION AND NUTRITIONAL INTERVENTIONS IN COLORECTAL CANCER (K WU, SECTION EDITOR)

Insights Into the Relationship Between Gut Microbiota and Colorectal Cancer

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Published online: 22 October 2018

Abstract

Purpose of review There is growing evidence to suggest that gut microbiota plays an important role in colorectal carcinogenesis. Western diet is associated with gut microbial dysbiosis, which leads to inflammation, oxidative stress, and genotoxic effects, all common risk factors for colorectal cancer.

Recent findings *Fusobacterium nucleatum*, *Helicobacter pylori*, *Bacteroides fragilis*, *Escherichia coli*, *and Streptococcus bovis* are the main bacterial species associated with colorectal carcinogenesis. Gut microbiota transforms both diet- (meat, processed meat products, fat) and host (bile acids)-derived precursors into carcinogens and further interferes with anti-cancer drug metabolism, chemotherapy efficacy, and drug-induced toxicity. Nutritional interventions, as well as the administration of beneficial bacteria (probiotics), dietary fiber (including prebiotics) supplements, and synbiotics (probiotic + prebiotic), may reduce the risk of colorectal cancer and side effects of anti-cancer therapy.

Summary Current evidence suggests gut microbiota may predispose or protect against colorectal cancer. Restoring gut microbial dysbiosis is an emerging nutritional and clinical target in oncology.

Keywords Gut microbiota · Colorectal cancer · Anti-cancer treatment · Probiotic · Prebiotic · Synbiotic

Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed cancer with an estimated 1.4 million cases and 693,900 deaths (~8.5% of total cancer deaths) occurring in 2012 worldwide [1]. In addition, CRC diagnosis is expected to increase by 60% with more than 2.2 million new cases and 1.1 million cancer deaths by 2030 [1]. According to the American Cancer Society, the total economic impact of premature death and disability from cancer worldwide, which does not include direct costs of treating cancer, was $895 billion in 2008 [2]. CRC is the second type of cancer that causes the most economic impact globally (~$99 billion) [2].

Most of CRC cases develop spontaneously (70–85%) and causes are multifactorial [3]. High consumption of saturated fatty acids, red, and processed meat, alcohol, and smoking habit and low consumption of dietary fiber are considered important factors in spontaneous CRC development [4, 5]. These lifestyle patterns are also associated with gut microbial dysbiosis [6–8]. Gut dysbiosis is an imbalance or maladaptation of the microbial communities which is deleterious to health [9]; furthermore, it is associated with high gut permeability and bacterial translocation [10]. This scenario leads to inflammation and genotoxic effects mediated by oxidative stress [6, 11]. Therefore, restoring the alteration of gut microbiota is an emerging nutritional and clinical target for the prevention and treatment of gut microbiota-related diseases, such as CRC.

This Article is part of the Topical Collection on *Nutrition and Nutritional Interventions in Colorectal Cancer*

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Although Hippocrates stated "…death sits in the bowels..."and "...bad digestion is the root of all evil...." in 400 B.C [12], gut microbiota was a neglected topic before the early 2000s [13]. However, emerging evidence suggest an important and independent impact of gut microbiota on health and disease [13]. It is estimated that the number of bacteria and human cells in our body is similar, and the relevant volume for the high bacteria density of 10^{11} bacteria/g is only that of the colon [14]. As such, it is likely that the gastrointestinal microbiome not only has the greatest impact on overall health and metabolic status of all microbiomes in the human body, but it also serves as a model for understanding the relationship between host-microbiota interactions and disease [6]. This review aims to highlight the associations between gut microbiota and CRC, its importance during anticancer therapy, and new dietary strategies and clinical interventions focusing on gut microbiota in patients with CRC.

Gut Microbiota and Risk for Colorectal Cancer

The association between bacteria and CRC was first suggested in the early 1950s as a case report [15]. Subsequently (mid 1970s), this hypothesis became stronger based on findings that germ-free rats developed fewer colonic tumors compared to conventional rats after tumor induction and that antibiotic administration reduced tumor development [6]. This observation was followed by a number of culture-based studies between the 1970s and 1990s that identified the microbial signatures associated with colon cancer risk [16]. Although these early studies suggested an association between microbes and cancer risk, the advent of culture-independent sequencing studies provided detailed insight on altered gut microbiota in patients with cancer. Overall, the literature suggests an overrepresentation of putative cancer-inducing microbial species with an underrepresentation of bacteria that have beneficial functions in human's health and in the metabolism of nutrients/drugs, antimicrobial protection, immunomodulation, and integrity of the gut barrier [17, 18•]. Thus, dysbiosis appears to be the link between microbiota and tumorigenesis [19, 20].

Dysbiosis has been associated with CRC and may promote tumor in spontaneous, genetically induced or carcinogen-induced CRC [6]. Mice fed with stool samples from patients with CRC increased the number of polyps, levels of intestinal dysplasia, and proliferation in colon compared with those fed with stool from healthy individuals, implying a cause-effect relationship [21•]. Potential mechanisms involved in CRC development are the production of bacterial-derived genotoxins or bacterial virulence factors, microbial-derived metabolism, host defense modulation, inflammation, and oxidative stress [7].

Some strains of bacteria have virulence factors and ability to penetrate intestinal epithelial cells, increasing CRC risk [7]. *Fusobacterium* spp. (gram-negative bacterium), especially *F. nucleatum* strains express fibroblast activation protein 2 (FAP2) and FadA on their surface [22, 23]. FadA binds to E-cadherin and activates β-catenin signaling, activating pro-inflammatory and oncogenic signals [22]. *F. nucleatum* can also promote a proinflammatory microenvironment by signaling p38 mitogen-activated protein kinase (MAPk) [24] or binding to toll-like receptors (TLRs) [25]. This proinflammatory microenvironment accelerates tumor progression [6, 7, 13, 24]. In addition, FAP2 suppresses immune cell activity through interacting with receptor T cell immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domain (TIGIT) and protects tumors from host immune cell attack [23]. *F. nucleatum* has been detected at approximately 36.2% in fecal analysis of patients with CRC and 16% in controls, using 16S rRNA sequencing [26]. In tumor tissue analysis, *F. nucleatum* was positivity associated histological grade [27] and lymph node metastases [28], suggesting its association with CRC progression and metastasis. Furthermore, a recent study conducted with fecal samples from 903 individuals showed the ratio of *F. nucleatum* to the beneficial bacteria *Faecalibacterium prausnitzii* and *Bifidobacterium* as a biomarker for screening early CRC [29].

Helicobacter pylori is a gram-negative bacterium strongly associated with gastric cancer [30] and classified as a group I carcinogen according to the International Agency for Research on Cancer [31]. The etiopathogenetic role of *Helicobacter pylori* in CRC has not been as well established as in gastric cancer [32]. However, this bacterial strain has been found in malignant tissue (~ 80%) and polyp tissues (~ 60%) of patients with CRC [33]. A meta-analysis showed that *Helicobacter pylori* infection is associated with CRC, although a significant heterogeneity across studies was found [34]. Epplein et al. [35] associated CRC risk with specific *Helicobacter pylori* proteins seropositivity, which are considered virulence factors (vacuolating cytotoxin A (VacA), hypothetical protein HP231, hypothetical protein HP305, neutrophil activating protein A (NapA), and helicobacter cysteine-rich protein C (HcpC)) versus the presence of *Helicobacter pylori* [32]. *Helicobacter pylori* produces two toxins, VacA and a bacterial cytotoxin–associated gene A (CagA) with the ability to interact with host cell components, therefore promoting proinflammatory cytokine production and cellular alterations via MAPk and E-cadherin/b-catenin [36]. Some of these functions are summarized in Fig. 1.

Another bacterial toxin associated with CRC is enterotoxigenic *Bacteroides fragilis* (ETBF) produced by *Bacteroides fragilis*, a gram-negative bacterium. This toxin is also present more frequently in the colon mucosa of patients with CRC (left colon 85.7% and right colon 91.7%) compared to controls (left colon 53.1% and right colon 55.5%) [37]. This result has also been confirmed in stool samples, but higher sensitivity methods are needed for better detection [38]. ETBF induces E-cadherin degradation (higher gut permeability), the polyamine catalyst spermine oxidase (SMO) (higher reactive

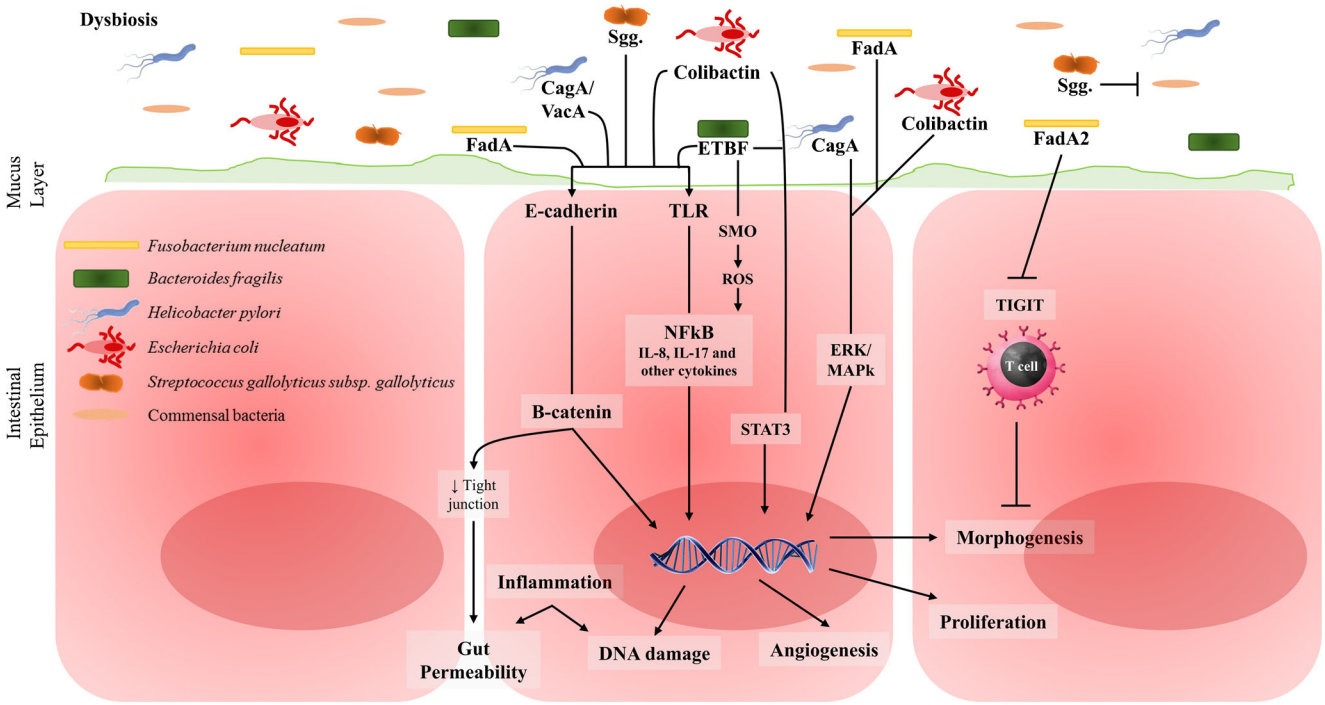

Fig. 1 Bacteria CRC-promoting and progression mechanisms. Toxins present in *Fusobacterium nucleatum* (FadA), *Helicobacter pylori* (CagA and VacA), *Escherichia coli* (colibactin), Enterotoxigenic *Bacteroides fragilis* (ETBF), and *Streptococcus gallalyticus* (Sgg.) activate the inflammatory pathway by toll-like receptor (TLR) and consequently nuclear factor kappa B (NFkB) which result in DNA damage, tumor proliferation, and gut permeability. The inflammatory process is upregulated by the polyamine catalyst spermine oxidase (SMO) concentrations which increase the production of reactive oxygen species. Toxins are also capable to bind E-cadherin on intestinal epithelial cells to activate β-catenin reducing thigh junctions and increasing gut permeability. Colibacatin and ETBF activate the signal transducer and activator of transcription 3 (STAT-3) that play a central role on tumor development and progression. FadA, Colibactin, and CagA are also enrolled with extracellular signal-regulated protein kinase and mitogen-activated protein kinase (ERK/MAPK) activation and subsequently proliferation and angiogenesis. Fibroblast activation protein 2 (FAP2) expressed by *Fusobacterium nucleatum* suppresses immune cell activities through interacting with receptor TIGIT (T cell immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domain) and consequently protects tumors from host immune cell attack. Sgg. can promote dysbiosis by killing commensals bacteria and increase cancer promoting bacterium

oxygen species production, DNA damage, and cell proliferation), and proinflammatory chemokines release (such as IL-8 and TNF-α, among others) by NF-κB and MAPk signaling [39]. The mucosal inflammatory immune response is also associated with higher Th17 response, which results in IL-17 production, a potent chemoattractant for neutrophils [39, 40].

Escherichia coli (*E. coli*) is a gram-negative bacterium usually found in the intestine and divided into four main phylotypes (A, B1, B2, and D) [41]. Phylotype A contains mostly commensal *E. coli* strains while phylotype B2 strains are frequent carriers of virulence genes [41]. Virulence genes strains have adherent-invasive property and produce different types of toxins as cytolethal distending toxin (CDT), colibactin, cytotoxic necrotizing factor (CNF1), and cycle inhibiting factor (CIFs) [42, 43]. However, colibactin is the genotoxin mostly associated with CRC due to the promotion of genomic instability and DNA damage [42, 43]. This toxin increases inflammation and releases growth factors mediated by senescence cells which are associated with cell proliferation [43]. Additionally, stool samples from patients with CRC were described as rich in *E. coli* compared to healthy and advanced adenoma samples and showed a positive association with C-reactive protein [44].

Streptococcus bovis is a gram-positive bacterium that received a new taxonomic classification after new species were discovered [45]. *Streptococcus bovis* biotype I was renamed as *Streptococcus gallolyticus* subspecies *gallolyticus*, and its infection could be found in 25 to 80% of patients with colorectal tumors [46]. A meta-analysis showed a significant association between *Streptococcus bovis* endocarditis (OR = 14.54, 95% CI 5.66–37.35), *Streptococcus bovis* septicemia (OR = 7.48, 95% CI 3.10–18.06), and CRC. In addition, feces from patients with CRC had a high incidence of *Streptococcus bovis* (OR = 2.52, 95% CI 1.14–5.58) [47]. The mechanisms attributed to the association between *Streptococcus bovis* and CRC include the overproduction of inflammatory markers, angiogenic factors, pro-oxidative reactive oxygen, and nitrogen species, contributing to the cellular proliferation and neoplastic processes by modifying cellular DNA [46]. According to Pasquereau-Kotula et al. (2018), *Streptococcus gallolyticus* subspecies *gallolyticus* can act as a cancer promoting bacterium, as mentioned above, or indirectly, secreting a

"bacteriocin" that can kill gut commensals and enable colonization with harmful microbes [48, 49].

The bacteria CRC-promoting mechanisms are shown in Fig. 1. Additional bacterial pathogens such as *Enterococcus faecalis* and *Clostridium septicum*, both gram-positive bacteria, have been associated with CRC [7, 50]. However, no clear epidemiological link to human carcinogenesis has been established, and the literature remains scarce. Other pathobionts (microorganisms of the microbiota that exert inflammation associated with the development of clinical disease), not directly associated with CRC, exhibit a proinflammatory activity and have been associated with inflammatory bowel diseases in humans (e.g., *Bacteroides*, *Enterobacteriaceae*, *Enterococcus*, *Escherichia*, *Shigella*, *Klebsiella*, *Streptococcus*, *Peptostreptococcus*, and *Clostridium difficile*) [51, 52]. In fact, chronic intestinal inflammation is the primary risk factor for the development of CRC (OR 5.7, 95% CI 4.6–7.0) [53]. On the other hand, patients with inflammatory bowel diseases have a reduction in *Faecalibacterium prausnitzii*, *Leuconostocaceae*, *Odoribacter splanchnicus*, *Phascolarctobacterium*, and *Roseburia*, which are producers of short-chain fatty acids (SCFA: acetate, propionate, and butyrate) [51, 52]. SCFA are produced by gut microbial organisms from dietary fiber consumption and have potential anti-carcinogenic and anti-inflammatory properties [54•]. Gut dysbiosis is generally associated with low production of SCFA and promotes mucus degradation and endotoxemia, factors associated with inflammation, and increased CRC risk [54•].

Diet, Microbiota, and Colorectal Cancer

As mentioned earlier, diet plays a particularly important role in CRC carcinogenesis. Pro-carcinogenic dietary compounds can be metabolized by gut microbiota, contributing to systemic inflammation, toxic metabolite production, and heterocyclic amine activation [55••]. Pro-carcinogenic compounds can be found in Western dietary pattern, which has been associated with increased CRC risk [4]. Meta-analyses have shown an inverse association between CRC and the consumption of vegetable and fruits [56, 57], whole grains [57], cruciferous vegetables [57, 58], and positive associations with high intake of red and processed meat [57, 59] and heavy consumption of alcohol [60]. This diet is also associated with low microbial diversity and gut dysbiosis [18•]. Additionally, the susceptibility to adherent-invasive *E. coli* infection and intestinal inflammation has been shown to increase with Western diet [61]. On the contrary, the consumption of whole grains and dietary fiber have been associated with a lower risk for *Fusobacterium nucleatum*–positive CRC [62] or inhibition of ETBF adherence and/or invasion into the mucosa [63].

Recent evidence suggests that the Western diet–induced systemic inflammation is maintained even after shifting mice to the control diet [64]. This inflammation may be driven by gut microbiota and is associated with mucus layer impairment and low SCFA production [54•]. An animal-based diet (rich in fat and protein) reduces bacteria responsible to produce SCFA (*Roseburia*, *Eubacterium rectale*, and *Ruminococcus bromii*) [65]. In addition, red and processed meat have several potential components associated with CRC (e.g., heme iron, lipid oxidation products, heterocyclic aromatic amines, polycyclic aromatic hydrocarbons, *N*-nitroso compounds), and gut microbiota can interact with them [66]. Experimental studies have shown that gut microbiota facilitates heme-induced hyperproliferation by opening the mucous barrier, bioactivating heterocyclic aromatic amines, and increasing the metabolite PhIP-M1 (5-methyl-3-phenyl-6,7,-8,9,-tetrahydropyridol[3′,2′:4,5]imidazo[1,2-a]pyrimi-din-5-ium chloride), mechanisms enrolled with cancer development [66]. Interestingly, a systematic review of experimental studies highlighted the insufficient evidence to confirm a mechanistic link between consumption of red meat as part of a healthy dietary pattern and CRC risk [67].

On the other hand, a possible explanation for the association with high fat intake and CRC may be attributed to high bile secretion and fractions (primary bile acids) that escape from reabsorption. Bile salt hydrolases found in all major bacterial divisions and the methanogenic archaea converts the primary bile acids into secondary bile acids (e.g., deoxycholic acid and lithocholic acid). High concentrations of secondary bile acids are associated with oxidative stress, inflammation, and carcinogenesis [54•]. The metabolism microbial also can contribute to alcohol toxicity. Oral and gut microbiota contribute to the production of acetaldehyde from ethanol which is highly toxic and carcinogenic [54•].

Gut Microbiota in Patients Undergoing Treatment for Colorectal Cancer

Gut microbiota affects drug metabolism, efficacy to chemotherapy, and drug-induced toxicity (Fig. 2) [68•]. Bacteria can interfere directly or indirectly on the metabolism of anticancer drugs; for example, the absence of bacteria may decrease response to immunotherapy, and on the other hand, the presence of specific microbes may interfere with treatment through their metabolic activities [69•]. Westman et al. showed that *Streptomyces* WAC04685 inactivated doxorubicin, via deglycosylation, reducing the therapy efficacy [70]. Gut microbiota has also been shown to interact with other types of commonly used drugs (e.g., sorivudine, an antiviral drug), and its co-administration with 5-fluorouracil (chemotherapic) may lead to severe toxicity and death [71].

β-Glucuronidase, an enzyme produced by bacteria that converts conjugated bilirubin to the unconjugated form for reabsorption, is also associated with toxicity. Its activity is higher in patients with CRC than healthy individuals and

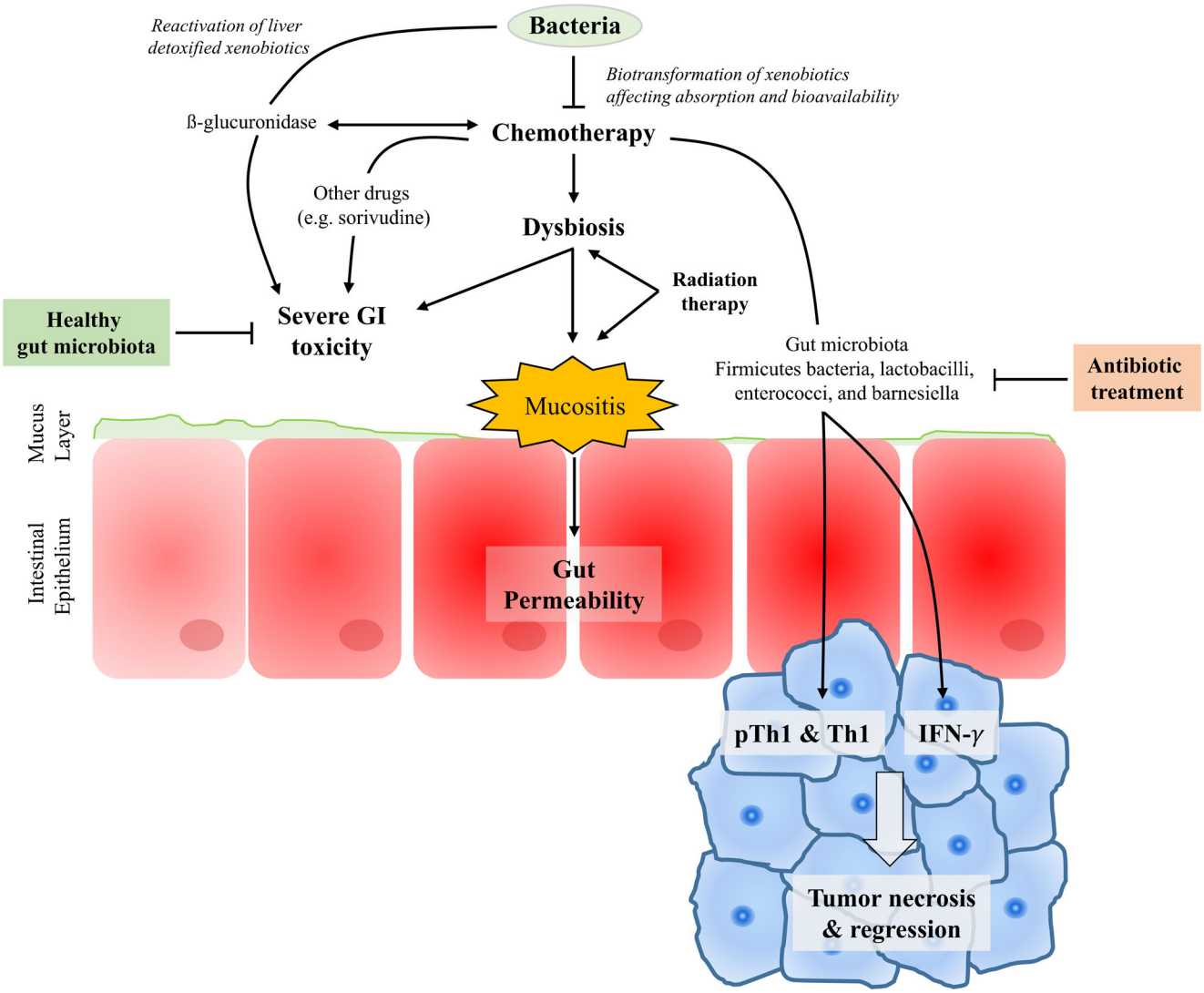

Fig. 2 The interaction of gut microbiota and anti-cancer treatment. Bacterial microbes can reduce the efficacy of chemotherapy (biotransformation, absorption, and bioavailability) or significantly increase its potential by β-glucuronidase bacteria-enzyme promoting severe gastrointestinal (GI) toxicity. Chemo- and radiation therapies also increase the GI toxicity by dysbiosis. Mucositis, an important outcome of anti-cancer therapies, increases gut permeability and consequently leads to a greater T helper 1 (Th1) immune responses, production of pathogenic T helper 17 cells (pTh17), and interferon gamma (IFN-γ) promoting tumor necrosis and regression. A healthy microbiota can decrease severe GI toxicity rates and help in anti-cancer treatment which can be inhibited by antibiotic treatment

may be induced by bile secretion and *E. coli* [72]. Irinotecan can be reconverted in active form during gut excretion by bacterial ß-glucuronidase, producing severe intestinal toxicity and diarrhea [73]. This drug also increases the abundance of ß-glucuronidase-positive bacterial species (*Clostridium* cluster XI and *Enterobacteriaceae*) in the proximal colon [74]. ß-Glucuronidase activity has been found in the Firmicutes phylum, particularly within *Clostridium* clusters XIVa and IV in the human gut [75, 76]. Therefore, strategies to inhibit this enzyme may potentially protect patients from toxicity [77].

In vitro, the presence of non-pathogenic *E. coli* or *Listeria welshimeri* inhibited the activity of ten anti-cancer drugs and enhanced the efficacy of six others [78]. On the other hand, commensal bacteria are important for the success of anti-cancer therapy [68•, 79, 80]. Lower anti-tumor efficacy was observed in antibiotic-treated and germ-free mice receiving cyclophosphamide [79]. The presence of gut microbiota was indispensable for the production of pathogenic T helper 17 cells (pTh17) and memory Th1 immune responses, reducing the tumor resistance to this drug. In these animals, dysbiosis occurred within 7 days of chemotherapy administration, with a reduction in Firmicutes bacteria, lactobacilli, and enterococci [79]. These results were corroborated in mice transplanted with cancer cell lines under the skin, a site distant from the gut microbiota [80]. The production of cytokines was lower in tumor-infiltrating myeloid-derived cells after immunotherapy (the cytosine, guanosine, phosphodiester link [CpG] oligonucleotides) and low cytotoxicity after oxaliplatin chemotherapy

was observed in antibiotic-treated and germ-free mice. Therefore, tumors from these mice did not respond as well to the therapy as did those from the control mice [80].

Bacteria strain associated with better chemotherapy response have been studied. The loss or limited efficacy of cyclophosphamide during antibiotic treatment and cancer-induced dysbiosis was restored by *Enterococcus hirae* and *Barnesiella intestinihominis*. *Enterococcus hirae* induced differentiation of Th17 and pTh17 cells in secondary lymphoid organs (such as spleen and lymph nodes), and *Barnesiella intestinihominis* promoted infiltration of IFN-γ-producing γδT cells in colon cancer lesions [81]. The administration of other bacteria strains has also been linked with improvement in anti-cancer therapy and will be described next.

Anti-cancer therapies alter gut microbiota composition and cause damage to the mucus layer, which disrupts barrier integrity and enables bacteria to penetrate the lamina propria, which lies beneath the epithelium [68•]. In an experimental study, Forsgård et al. showed that common drugs used for CRC treatment (5FU, oxaliplatin, and irinotecan) increased intestinal permeability and this correlated with the severity of chemotherapy-induced gastrointestinal toxicity and pathologies such as diarrhea, pain, weight loss, and infections [82]. In addition, these drugs induced several microbial and metabolic changes, which activated inflammatory processes, potentially playing a role in the pathophysiology of chemotherapy-induced gastrointestinal toxicity [83].

Radiation therapy also promotes dysbiosis and increases gut permeability and is positively associated with severe gastrointestinal toxicity [84, 85]. Intestinal mucositis and enteropathy hinder radiation therapy [86]. These side effects increase the translocation of gut pathobionts to systemic tissue and triggers systemic innate and adaptive immunity, leading to local inflammation [84, 85]. Interestingly, the radiation dose could be higher and the gastrointestinal toxicity low depending of the gut microbiota [87]. Therefore, gut microbiota appear to play an important role in the success of anti-cancer therapy; however, the inflammatory process may be elevated in the presence of pathobionts, leading to severe gastrointestinal toxicity.

New Dietary Interventions in Patients With Colorectal Cancer

Dietary supplements such as probiotics, prebiotics, and synbiotic have been suggested to reduce CRC risk and the severity of anti-cancer therapy gastrointestinal toxicity [88–90]. However, experimental studies in animals are mostly used to confirm these benefits [91•]. Few randomized clinical trials have been conducted as shown in Table 1 based on a PubMed search (January 2012 to July 2018) using the following MeSH terms: probiotic, prebiotic, synbiotic, dietary fiber, or resistant starch combined with colorectal cancer (articles published in English).

Probiotics have anti-cancerous and anti-mutagenic activity [88–90]. Beneficial microbes can bind to mutagen, help biotransformation and degradation of carcinogens, inhibit mutagenesis, enhance the host immune system, and produce lactic acid and SCFA, which decreases harmful bacteria [88–90].

A mix of probiotics containing *Bifidobacterium longum*, *Lactobacillus acidophilus*, and *Enterococcus faecalis* (1:1:1) with a dose of 6.0×10^7 CFU/g viable cells for 5 days, three times/day, was able to increase the density and diversity of mucosal microbes and reduce the abundance of the genus *Fusobacterium* [92]. However, the authors noted that a short-term administration of these bacteria cannot achieve a significant clinical effect.

In an open, randomized, parallel-group clinical trial with ETBF carriers, a yogurt supplemented with a probiotic strain (*Bifidobacterium longum* BB536) reduced the ETBF after 8 weeks compared to the control group receiving milk [93]. The authors speculated a direct effect of probiotic on ETBF growth and an indirect effect via modulating epithelial-derived antimicrobials.

Beneficial effects of probiotics on the mitigation of chemotherapy side effects [94, 95] and complications after gastrointestinal surgery (e.g., septicemia and time until hospital discharge) [96–101] have been reported. After 8 weeks of a probiotic mix supplementation, patients with CRC improved quality of life and reduced inflammation and chemotherapy side effects (e.g., fatigue, nausea, vomiting, diarrhea, dry mouth, taste alteration) [94]. However, the effects on inflammation could not be exclusively attributed to the mix of probiotics due to the concurrent use of omega-3 fatty acid at 2 g/day [94]. The second 12-week study testing the effect of probiotics during chemotherapy showed a reduced incidence of severe diarrhea, enterocolitis, and the use of antidiarrheal drugs [95].

Protocols for probiotic supplementation studied in patients with CRC undergoing surgery varied substantially [96–101]. In most protocols, probiotic supplementation started before surgery and continued after the operation. One study tested the effect of supplementation on complications after gastrointestinal surgery with one bacterial species [101]. Studies conducted with a mix of probiotics showed reductions in hospital discharge [96, 97], postoperative complications (e.g., infections, septicemia) [97–100], gut permeability [98, 99], and inflammation [98–100]. In addition, a faster return of normal gut function was observed [96], as well as an improvement in immune response and in the amount of *Bifidobacterium* in feces [100]. On the other hand, the study performed with *Bifidobacterium bifidum* supplementation reported an increase in postoperative complications and rates of leakage [101].

In a randomized, double-blind, placebo-controlled study with CRC survivors (stages II–III) who completed treatments between 6 weeks and 2 years prior, probiotics reduced irritable

Table 1 Randomized clinical trials testing the effect of probiotics, prebiotics and synbiotic on colorectal cancer

Ref.	Study design	Treatment	Study period	Sample size	Results vs. placebo
Probiotics					
[92]	Randomized placebo-controlled	*B. longum*, *L. acidophilus* and *Enterococcus faecalis* (6.0×10^7 CFU), 3×/day	5 days	22 patients with CRC undergoing to radical colorectomy matched by sex, age, BMI, cancer stage, and time between onset of symptoms and hospital admission	↑ Density and diversity of mucosal bacteria ↓ *Fusobacterium*, *Peptostreptococcus*, *Comamonas*, and expansion of *Enterococcus* and *Proteobacteria* in the mucosa-adherent microbiota
[93]	Randomized, parallel group	160 g of yogurt containing *Lactococcus lactis*, *S. thermophilus*, and *L. delbrueckii* subsp. *Bulgaricus* (1.0×10^9 CFU of lactic acid bacteria) enriched with *B. longum* BB536 ($4.27 \pm 1.25 \times 10^8$ CFU)	8 weeks	32 patients ETBF carriers matched by sex, age, BMI, and with yogurt intake less than twice per week	↓ ETBF ↓ *B. fragilis*, *Bacteroides ovatus*, and *Bacteroides vulgatus*
[94]	Randomized, double-blind, placebo-controlled	*L. acidophilus* BCMC 12130, *L. casei* BCMC 12313, *L. lactis* BCMC 12451, *B. bifidum* BCMC 02290, *B. longum* BCMC 02120, and *B. infantis* BCMC 02129 (60 billion CFU) + omega-3 fatty acid (2 g/day)	8 weeks	140 patients with CRC on chemotherapy (capecitabine and oxaliplatin) matched by sex, age, BMI, CRC location, ethnic, education level, marital status, family history	↑ Quality of life ↓ IL-6 and side effects of chemotherapy (e.g., fatigue, nausea, vomiting, diarrhea, dry mouth, taste alteration)
[95]	Randomized, double-blind, placebo-controlled pilot study	*B. breve* HA-129 (25%), *B. bifidum* HA-132 HA (20%), *B. longum* HA-135 (14.5%), *L. rhamnosus* HA-111 (8%), *L. acidophilus* HA-122 (8%), *L. casei HA*-108 (8%), *L. plantarum* HA-119 (8%), *S. thermopilus* HA-110 (6%), *L. brevis* HA-112 (2%), *B. infantis* HA-116 (0.5%) (10×10^9 CFU)	12 weeks	46 patients with CRC on chemotherapy (irinotecan) matched by age, sex, line of therapy, primary tumor and resection of the primary tumor	↓ Incidence of severe diarrhea (grade 3 or 4) ↓ Overall incidence of diarrhea ↓ Incidence of enterocolitis ↓ Antidiarrheal drugs
[96]	Randomized, double-blind, placebo-controlled	*L. acidophilus* BCMC 12130, *L. casei* BCMC 12313, *L. lactis* BCMC 12451, *B. bifidum* BCMC 02290, *B. longum* BCMC 02120, and *B. infantis* BCMC 02129 (60 billion CFU)	7 days pre-surgery	40 patients with CRC undergoing to elective surgery matched by age, sex, and tumor stage	↑ Return of normal gut function* ↓ Time until hospital discharge
[97]	Randomized, double-blind, placebo-controlled pilot study	*L. acidophilus* LA-5 1.75×10^9 CFU, *L. plantarum* 0.5×10^9 CFU, *B. lactis* BB-12 1.75×10^9 CFU *and Saccharomyces boulardii* 1.5×10^9 CFU, 2×/day	1 day pre and 15 days post-surgery	164 patients with CRC undergoing to colorectal surgery matched by age, sex, type of surgery, and comorbidities	↓ Risk of postoperative complications ↓ Time until hospital discharge
[98]	Randomized, double-center, double-blind, placebo-controlled	*L. plantarum* ($\geq 10^{11}$ CFU/g), *L. acidophilus*-11 ($\geq 7.0 \times 10^{10}$ CFU/g) and *B. longum*-88 ($\geq 5.0 \times 10^{10}$ CFU/g), 2 g per day	6 days pre- and 10 days post-surgery	134 patients with colorectal liver metastases undergoing to surgery matched by age, sex, BMI, location of tumor, and biochemical tests	↓ Serum zonulin and plasma endotoxin levels ↓ Rate of postoperative septicemia ↓ Rate of positive bacterial cultures (*Escherichia coli*, *Staphylococcus aureus*, and *Aeruginosin*)
[99]	Randomized, double-center, double-blind, placebo-controlled	*L. plantarum* ($\geq 10^{11}$ CFU/g), *L. acidophilus*-11 ($\geq 7.0 \times 10^{10}$ CFU/g) and *B. longum*-88 ($\geq 5.0 \times 10^{10}$ CFU/g), 2 g per day	6 days pre- and 10 days post-surgery	150 patients with CRC undergoing to a radical colectomy matched by age, sex, BMI, location of tumor, medications, and biochemical tests	↓ Serum zonulin levels ↓ Rate of postoperative septicemia ↓ Bacterial translocation, intestinal permeability ↓ p38 MAPK signaling pathway

Table 1 (continued)

Ref.	Study design	Treatment	Study period	Sample size	Results vs. placebo
					↓ Rate of positive bacterial cultures (*Escherichia coli* and *Staphylococcus aureus*)
[100]	Randomized, placebo-controlled	*B. longum*, *L. acidophilus*, and *Enterococcus faecalis*, (1.9×10^8 CFU)	3 days pre-surgery	60 patients with CRC undergoing to a radical colorectal resection matched by age, sex, BMI, site of tumor and procedure received, cancer stage, and biochemical tests	↓ Infectious complications ↑ *Bifidobacterium* in feces ↓ *Escherichia* in feces ↓ Endotoxin, D-lactic acids, serum IL-6, and CRP ↑ Serum IgG and sIgA
[101]	Prospective randomized trial	*B. bifidum* (10^9 CFU)	7 days pre and postoperative day 5 for 10 days	294 colon cancer patients undergoing to elective surgery matched by age, sex, tumor site, type of surgery, preoperative condition	↑ Rates of incisional surgical site infection ↑ Rates of leakage ↔ *Clostridium difficile* toxin ↑ *Bifidobacterium, Bacteroides fragilis group, Escherichia/Shigella group* in feces on postoperative day 7
[102]	Randomized, double-blind, placebo-controlled	*L. rhamnosus* R0011, *L. acidophilus* R0052 (2×10^9 CFU)	12 weeks	60 CRC survivors in stage II-III matched by age, sex, BMI, quality of life, irritable bowel symptoms, life style factors, location of tumor, and treatment	↓ Irritable bowel symptoms ↑ Cancer-related quality of life ↑ Functional well-being scores
Prebiotics					
[103]	Randomized controlled diet	Heat-stabilized rice bran (30 g/day)	28 days	19 CRC survivors matched by age, sex, BMI, and calories intake	↑ Hesperidin (28-fold) and narirutin (14-fold) in stool samples ↑ Fatty acid, leucine/valine, and vitamin B_6 metabolic pathways in stool ↓ AGE, steroid metabolism, primary bile acid metabolism pathway in stool
[104]	Randomized controlled pilot clinical trial	Heat-stabilized rice bran powder (30 g/day) or cooked navy bean powder (35 g/day)	28 days	29 overweight/obese patients with a prior history of CRC matched by macronutrient consumption	↑ Gut bacterial diversity and altered gut microbial composition at 28 days ↓ Firmicutes:Bacteroidetes ratio (rice bran group) ↑ SCFA (propionate and acetate) in stool after 14 days (rice bran group)
[105]	Randomized controlled	30 g resistant starch or 600 mg aspirin	Up to 4 years	937 participants with lynch syndrome matched by age, sex, geographic region, and follow-up	↔ Development of primary colorectal cancers ↔ Protective effect on colorectal cancer
[106]	Randomized, double-blind, placebo-controlled	Double-intervention group: 23 g high-amylose corn starch and 12 g polydrextrose	50 days	29 microRNAs of colorectal mucosal biopsies from healthy participants matched by age, sex, BMI, ethnicity, endoscopy procedure, smoke status	↑ Micro-RNA miR-32 expression
[107]	Randomized, double-blind, placebo-controlled	Resistant starch group: 23 g high-amylose corn starch and 12 g maltodextrin or Polydextrose group: 12 g polydrextrose 23 g corn starch or Double-intervention group: 23 g high-amylose corn starch and 12 g polydrextrose	50 days	75 healthy participants matched for age, sex, BMI, ethnicity, smoking status, and procedure	↔ Calprotectin, an indicator of inflammation in the large bowel ↓ SFRP1 mRNA expression in resistant starch and polydextrose
[108]	Randomized, cross-over,	07 units of dates, approximately 50 g	21 days separated	22 healthy participants	↓ Genotoxicity in human fecal water

Table 1 (continued)

Ref.	Study design	Treatment	Study period	Sample size	Results vs. placebo
	placebo-controlled		by a 14-day washout period		↔ Bacterial groups selected or SCFA
[109]	Randomized, double-blind, cross-over, placebo-controlled	300 g/day of cooked red meat with 40 g/day of butyrylated high-amylose maize starch	4 weeks separated by a 4-week washout period	23 healthy participants	↓ Formation of colorectal epithelial O6MeG adducts ↓ Epithelial proliferation Relative to its baseline: ↑ SCFA (20%) ↑ The abundances of *Clostridium coccoides*, *Clostridium leptum*, *Lactobacillus* spp., *Parabacteroides distasonis*, and *Ruminococcus bromii* ↓ *Ruminococcus torques* and the proportions of *Ruminococcus gnavus*, *Ruminococcus Torques* and *Escherichia coli*
[110]	Randomized, double-blind, cross-over, placebo-controlled	Wheat bran extract (10 g/day)	3 weeks separated by a 3-week washout period	20 healthy participants	↑ Colonic bacterial activity and/or growth ↓ Colonic protein ↑ Bifidobacteria ↔ Fecal water cytotoxicity nor with genotoxicity
[111]	Randomized, controlled cross-over	300 g/day of cooked lean red meat with 40 g/day of butyrylated high-amylose maize starch	4 weeks, separated by a 4-weeks washout period	23 healthy participants	↑ Fecal butyrate ↓ Levels of the oncogenic microRNA miR17–92 cluster in rectal mucosa ↑ *CDKN1A*
[112]	Randomized, double-blind, cross-over, controlled	*Lupinus angustifolius* cv. Boregine (blue lupin) or *Lupinus albus* cv. Typ top fiber (white lupin) or *Glycine max* cv. Hefeng fiber (soya), 25 g/day	2 weeks	78 healthy participants	↑ Daily fecal weight by blue and white lupin ↑ SCFA with blue and white lupin ↓ Fecal pH (blue lupin) ↑ Primary bile acid excretion (blue lupin) ↓ Fecal concentrations of total and secondary bile acids (blue lupin:16%; white lupin: 24%; soya: 16%)
Synbiotic					
[113]	Randomized, double-blind, placebo-controlled	*L. acidophilus* NCFM (2×10^9 CFU), *L. rhamnosus* HN001 (2×10^9 CFU), *L. paracasei* LPC-37 (2×10^9 CFU), *B. lactis* HN019 (2×10^9 CFU) and fructooligosaccharides 12 g, 2 ×/day	5 days pre- and 14 days post-surgery	91 colorectal adenocarcinoma patients with indication of elective and potentially curative colorectal resection matched by age, sex, BMI, ASA score, tumor stage, and biochemical tests	↓ Surgical site infection ↓ Overall infection
[114]	Randomized, double-blind, placebo-controlled	*Pediacoccus pentosaceus* 5–33:3, *Leuconostoc mesenteroides* 32–77:1, *L. paracasei* subsp. *paracasei* 19, and *L. plantarum* 2362 (10^{11} UFC) + 10 g of a prebiotic mix (2.5 g betaglucan, 2.5 g inulin, 2.5 g pectin, 2.5 g resistant starch)	15 days post-surgery	67 patients with CRC undergoing to elective colectomy matched by age, sex, BMI, tumor stage and location, chemotherapy, type of surgery, and gastrointestinal symptoms	↑ Gastrointestinal Quality of Life Index after 1, 3, and 6 months the surgery Improved diarrhea domain score
[115]	Randomized, controlled,	*Pediacoccus pentosaceus* 5–33:3, *Leuconostoc mesenteroides*	3 days before the surgery	54 patients with preceding large bowel operation for colorectal	↑ *Lactobacillus* on mucosa (synbiotic group)

Table 1 (continued)

Ref.	Study design	Treatment	Study period	Sample size	Results vs. placebo
	double-blind	32–77:1, *L. paracasei* subsp. *paracasei* 19, and *L. plantarum* 2362 (8×10^{11} UFC) + 20 g of a prebiotic mix (2.5 g betaglucan, 2.5 g inulin, 2.5 g pectin, 2.5 g resistant starch) or 20 g of a prebiotic mix		cancer matched by age, sex, and ASA score	↔ Systemic inflammatory response ↔ Postoperative course and complications

↑ increase, ↓ decrease, ↔ without effect, *CRC* colorectal cancer, *BMI* body mass index, *ETBF* enterotoxigenic *Bacteroides fragilis, B Bifidobacterium*, *L Lactobacillus*, S *Streptococcus*, *IL-6* interleukin-6, *CRP* C-reactive protein, *IgG* immunoglobulin G, *sIgA* soluble immunoglobulin A, *SFRP1* secreted frizzled-related protein 1, *SCFA* short-chain fatty acids, *ASA* the American Society of Anesthesiologists, *CDKN1A* cyclin-dependent kinase inhibitor 1A, *O6MeG* O6-methyl-2-deoxyguanosine

*Defined as at least 80% tolerance of an individual's daily caloric requirement

bowel symptoms and increased functional well-being scores and cancer-related quality of life. Future studies with fecal microbiota analyses will determine the potential underlying mechanisms behind this finding [102].

A recent meta-analysis showed that prophylactic probiotic administration associated with antibiotics had a superior effect compared to antibiotics alone in the prevention of surgical site infection after CRC surgery (RR 0.72; 95% CI 0.56–0.92; $P < 0.01$). Furthermore, a reduction in the incidence of diarrhea, abdominal distention, pneumonia, urinary tract infection, the cumulative duration of antibiotic therapy, and length of stay has been reported [116].

In regard to prebiotics, its most recent definition is "a nondigestible compound that, through its metabolization by microorganisms in the gut, modulates composition and/or activity of the gut microbiota, thus conferring a beneficial physiological effect on the host" [117]. This includes inulin, fructooligosaccharides, transgalactooligosaccharides, human milk, oligosaccharidase, and candidate prebiotics (e.g., resistant starch, pectin, arabinoxylan, whole grains, dietary fibers, and noncarbohydrates that exert their action through a modulation of the gut microbiota) [117]. Some anti-carcinogen properties of prebiotics might be similar to that of probiotics since the former stimulate the growth of beneficial bacteria [89, 90]. Furthermore, prebiotics can increase the production of SCFA and lactic acid, interfere in gene expression, and modulate immune system and enzymes that metabolize xenobiotics [89, 90].

The effect of prebiotics on CRC prevention was investigated on CRC survivors [103, 104], those with predisposition to the disease (e.g., lynch syndrome) [105] and in healthy individuals [106–112]. Similarly to probiotic studies, prebiotic studies were highly variable especially in terms of the amount and type of ingredient administered. Prebiotics increased the expression of hesperidin and narirutin in stool, (both are antioxidant and anti-inflammatory) compounds in CRC survivors. In addition, a reduction in the pathways of advanced glycation end-products (AGE), steroid metabolism, and primary bile acid metabolism in stool was observed after prebiotic consumption [103]. Prebiotics also modulated gut microbiota, reducing Firmicutes:Bacteroidetes ratio and increasing gut bacterial diversity and SCFA concentrations in overweight/obese patients with a prior history of CRC [104].

In patients diagnosed with lynch syndrome, also known as hereditary non-polyposis colon cancer, the administration of 30 g of resistant starch did not affect the development of primary CRC, nor promoted protective effect against the disease [105]. However, the authors described the absence of dietary fiber intake data as a potential limitation of the study and have also adjusted the analysis by geographical region trying to eliminate this influence, which may not have been required [105].

The effects of prebiotics on CRC risk has also been studied in healthy individuals by micro-RNA markers or by measuring fecal water genotoxicity, a non-invasive marker of CRC risk [106–112]. Two articles from the Dietary Intervention, Stem cells and Colorectal Cancer (DISC) Study did not observe any association between prebiotics and CRC risk [106, 107]. These studies showed that prebiotics increased microRNA miR-32 [106] and decreased the secreted frizzled-related protein 1 (SFRP1) [107] expressions in colorectal mucosa. However, the sample size was relatively small and further studies are needed to confirm these findings [106, 107].

Conversely, the administration of prebiotics in healthy individuals was capable to reduce CRC risk by reducing fecal water genotoxicity [108], or decreasing the formation of colonic O6-methyl-2-deoxyguanosine (O6MeG) adducts and expression of oncogenic microRNA miR17-92 cluster [109, 111] as well as reducing the fecal concentrations of total and secondary bile acids [112]. Prebiotics also increased SCFA concentrations [109, 111, 112] and improved gut microbiota [109, 110] in healthy individuals.

The concept of synbiotics emerged as a speculation of the benefits of concurrent supplementation of prebiotics and probiotics [90]. Synbiotics are defined as "a combination of probiotic bacteria and the growth promoting prebiotic

ingredient" which suggests a "synergism" [89, 90], which are nonetheless rarely observed in humans [118]. Whether this synergism can enhance the anti-carcinogenic potential of pro- and prebiotics is unknown.

Only three randomized controlled trials examined the effect of synbiotics use after CRC surgery [113–115]. Two of them showed positive effects on infections [113] and the gastrointestinal quality of life index [114]. The others lead to an increase concentration of *Lactobacillus* in the mucosa, but without an effect on postoperative course and complications [115].

A meta-analysis conducted with six randomized controlled trials estimated the efficacy of probiotic and synbiotic treatment in patients undergoing elective colorectal resection. Perioperative probiotic and synbiotic administration prevented diarrhea (OR 0.29, 95% CI 0.14 to 0.62, $P < 0.01$), the incidence of operative total infections (OR 0.39, 95% CI 0.22 to 0.68, $P < 0.01$), and pneumonia infection (OR 0.32, 95% CI 0.11 to 0.93, $P = 0.04$). In addition, the treatment increased *Lactobacillus* (MD 2.66, 95% CI 2.13 to 3.18; $P < 0.0001$), and decreased *Enterobacteriaceae* (MD − 1.52, 95% CI − 1.93 to − 1.11, $P < 0.0001$) in feces [119].

It is important to consider that number of studies analyzing gut or mucosa-adherent microbiota [92, 93, 100, 101, 104, 109, 110, 115] is extremely limited, but evidence that gut microbiota plays an important role in colorectal carcinogenesis is emerging. Further research on the association between gut microbiome and the mechanism of action of probiotics, prebiotics, and synbiotics as anti-carcinogenic agent are needed. Previous reviews [88–90] and meta-analyses [116, 119] have shown positive effects of probiotic, prebiotic, and synbiotic administration and suggested further human randomized clinical trials to elucidate the mechanisms and prove the effectiveness of these new dietary interventions in prevention and treatment of CRC.

Conclusions

Gut microbiota can play an important role in colorectal carcinogenesis and has also been shown to impact anti-cancer drug metabolism, chemotherapy efficacy, and drug-induced toxicity. However, establishing a cause-effect relationship between CRC and dysbiosis is challenging. It is possible that inflammation driven by gut microbiota and influenced by dietary patterns may play a role. Studies implicating microbes on CRC development are needed and could be conducted with humanized mice or in prospective studies.

Restoring the lack of beneficial bacteria in the gastrointestinal tract is an emerging nutritional and clinical target for the prevention and treatment of the CRC. Dietary changes, together with probiotics, prebiotics, and synbiotics, are considered interventions that may support these effects. However, many questions are still unclear such as the type of probiotic or prebiotic that may influence CRC development or progression. It is important to note that probiotics currently available on the market have not been designed to target cancer; novel probiotics should be developed based on recent sequencing work. Additionally, well-designed clinical trials are needed to identify the benefits of potential types of bacteria or prebiotic and its administration dose and timing in patients with CRC.

Funding Information C.M.P. is supported by a Canadian Institutes of Health Research (CIHR) New Investigator Salary Award and the Campus Alberta Innovates Program.

Compliance with Ethical Standards

Conflict of Interest The authors declare they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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