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## Role of diet and gut microbiota on colorectal cancer immunomodulation

De Almeida CV *et al.* Diet and gut microbiota on immune system

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## Abstract

Colorectal cancer (CRC) is one of the most commonly diagnosed cancers and it is characterized by genetic and epigenetic alterations, as well as by the infiltration of inflammatory cells among malignant and stromal cells. However, this dynamic infiltration, can be influenced by the microenvironment to promote tumor proliferation, survival and metastasis or cancer inhibition. In particular, the metabolites of cancer microenvironment are able to orchestrate the inflammatory cells, also developing a chronic inflammatory response that can be a predisposing condition for the CRC retention. In addition, some nutritional components might contribute to a chronic inflammatory condition, by regulating various immune and inflammatory pathways. Besides that, the diet strongly modulates the gut microbiota composition, which has a key role in maintaining the gut homeostasis and it is associated with the modulation of host inflammatory and immune responses. Therefore, diet has a fundamental role in CRC initiation, progression and mainly in prevention. In particular, functional foods as probiotics, prebiotics and symbiotics can have a potentially positive effect on health beyond basic nutrition and exhibit anti-inflammatory impacts. In this review, we discuss the influence of diet on the gut microbiota composition, focusing on its role on the gut inflammation/immunity. Finally, we describe the potential benefits of using probiotics and prebiotics in the modulation of host inflammatory response, as well as its application on the prevention and treatments of CRC.

**Key words:** Colorectal cancer; Diet; Inflammation; Immune response; Gut microbiota

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**Core tip:** The host immune system plays a central role in colorectal cancer (CRC) prevention and development. However, the immune response is deeply influenced by the gut microbiota composition, which in turn is modulated by the host diet. So, diet could be used as a strong ally to prevent CRC and to support its treatment.

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## INTRODUCTION

Inflammation consists of innate system with cellular and humoral responses to an injury induced by foreign organisms, dead cells or physical irritants stimulus. The aim is the attempting to inactivate the primary triggers and to regenerate the injured tissues. As a response to those injuries, a multifactorial network of chemical signals initiates and amplifies the recruitment of leukocytes (neutrophils, monocytes, and eosinophils) into the damage sites[1]. Nevertheless, when unregulated, the inflammatory process can become chronic with a persistent production of growth factors, reactive oxygen (RO) and nitrogen species (NS) that interact with the DNA of the cells. As result, we could identify permanent genomic alterations[2] that can lead the development of diseases, such as obesity[3], diabetes[4], and different cancer types[5,6].

 Inflammation has been considered a predisposing condition for tumor development since 1863[7,8] and nowadays, at least 20% of all cancers are considered to be a direct consequence of chronic inflammatory process[9]. Besides that, many malignancy aspects, are affected by cancer-associated inflammation[10-12]. A chronic inflammation persistently promotes a pro- tumorigenic microenvironment, which is rich in cytokines, the mainly players in regulating the crosstalk between malignant cells and the surrounding stromal cells[13].

 Chronic inflammatory disorders of the intestine, such as inflammatory bowel diseases (IBD), including Crohn’s disease (CD) and ulcerative colitis (UC), are considered to be a risk factor for colorectal cancer (CRC) since their initiation and progression are closely linked to the gene-environment and gene-gene interactions[14-17]. In this scenario, the inflammatory microenvironment is considered a crucial contributing factor to the CRC evolution[5,10,18,19]. Even being one of the most studied human malignancies; the CRC is still the third most common cancer worldwide with 140250 new cases estimated in 2018[20]. CRC occurs more frequently in high-income countries[21], mostly in sporadic forms, with only 25% of the cases having a familial feature[22]. Furthermore, the immune system also plays an important role in antitumor resistance[23].

 Since some nutritional components, such as saturated fats, refined carbohydrates, and red meat, may have pro-inflammatory properties, the World Cancer Research Foundation and the American Institute for Cancer Research consider diet as one of the most important exogenous factors in the CRC etiology[24-28]. In addition, epidemiological studies demonstrated that diet-gene interactions could cause diverse somatic alterations known to be involved with gastrointestinal cancers development. These distinct alterations could be associated with the wide variation of CRC risk and progression, among different individuals[29]. Besides that, food and nutritional aspects have a major impact on the modulation of host gut microbiota (GM)[30-32] which in turn have a crucial symbiotic relationship with the host by regulating its physiology and immune system, which make them important factor in health and disease.

 In this review, we point out the main aspects of CRC immunological scenario and the dietary impact on CRC-associated inflammation and GM modulation. Finally, we discuss the potential beneficial effects of probiotics and prebiotics administration to restore intestinal microbiota in the CRC prevention and as support of current anti-CRC treatments.

## IMPACT OF DIETARY HABITS AND LIFESTYLE IN CRC

Nowadays it is estimated that 30%-40% of the different cancers is caused by food, nutrition and other lifestyle factors, which make cancer a somewhat preventable disease. Overwhelming epidemiological data suggest that dietary factors, particularly those that result in overweight and obesity, influence risk, morbidity and mortality in multiple distinct cancers[33], especially CRC[29]. In sight of this assumption, the Department of Health and Human Services at National Institutes of Health and The Agency for Healthcare Research and Quality have attempted to implement lifestyle interventions among the population, aiming to alert the importance of diet and healthy lifestyle for the prevention of diseases, including cancer[34,35].

 However, although being considered an important source of mutagenic compounds (that may lead to tumor development)[36], differently from other environmental factors, such as UV in melanoma (of which the role on cancer was already well established), the diet components’ association with cancer might well be not so linear (Table 1). The link between nutrition and cancer can be muddled by other health-compromising factors such as smoking and alcohol consumption, sedentary lifestyle and exposure to environmental toxicants, all well established as risk factors for cancer development[37]. Thus, even if it is hard to ‘isolate’ dietary risk factors in epidemiological studies, animal models have irrefutably demonstrated the nutrition influences on cancer evolution[38]. Besides that, as resumed on Figure 1, diet components could act in an indirect way on cancer initiation and progression, by increasing the production of endocrine factors, or changing inflammatory and immunological parameters, or by changing the GM composition[37].

 Direct effects of dietary components on cancer development could be represented by the strong correlation between CRC incidence and excessive consumption of fats and proteins (mainly of animal sources), processed meat, and substantial alcohol consumption (more than 30 g/d)[39-41]. People are more susceptible to develop CRC when they have an increased intake of heterocyclic amines (HCA). The main HCA generated are 2-amino-1-methyl-6- phenyl-imidazo[4,5-b]pyridine (PhIP), 2-amino-3,8-dimethylimidazo[4,5-f] quinoxaline (MeIQx), and benzo[a]pyrene (Bap) a polycyclic aromatic hydrocarbon (PAH), the first reported group of chemical carcinogens for human cells[42]. Otherwise, vegetarian diet seems to prevent cardiovascular diseases, type 2 diabetes and cancer[43], since fruits and vegetables invariably contain antioxidants, which scavenge free radicals and prevent DNA damages[44]. The vegetarian diet also includes a variety of nutrients associated with reduction of cancer development risk[45]. These compounds can protect cells by affecting the bio-transformation/detoxification pathways (phases I and II), the cell signaling and endogenous antioxidant system[46]. Some micronutrients, such as zinc[47] and selenium[48], have been extensively studied and seem to have important roles in cancer prevention, whereas complex compounds such as carotenoids[49], flavonoids[50], curcumin and silymarin[51], resveratrol[52], folate[53] and total oligomeric flavonoids[54] show both direct activity against tumor cells and *in vitro* immunomodulatory effects.

 Besides that, nutrients such as glucose and amino acids increase the proliferative rate of tumor cells by activating the growth signaling proto- oncogenes such as IGF1R, PI3K, and AKT. In this way, deprivation of nutrients as well as nutrient-responsive growth factors seem to kill selectively high proliferative/resilient cancer cells by forcing their glycolytic asset toward an oxidative one. In fact, the calorie restriction (CR), defined as 30%–60% less of daily calorie requirement without malnutrition, is known to extend healthy life span with anticancer effects; being particularly effective in reducing the incidence, mass, and metastasis of breast cancer (due to the profound metabolic reprogramming that builds up adaptive stress responses)[55]. The controlled fasting also demonstrated to be a promising as adjuvant treatment in cancer therapy, mainly when associated with ketogenic diets (KD), that is low in carbohydrates and high in fats[56]. Moreover, short-term fasting exerts a beneficial impact on cancer immunosurveillance, since it induces the depletion of regulatory T cells, while an isocaloric diet with protein restriction has been demonstrated to induce an IRE1α-dependent UPR in cancer cells, enhancing cytotoxic CD8+ T cell (CTL). The presence of CTL in the tumor environment [tumor infiltrating lymphocytes (TIL)] is considered a positive outcome of the cancer treatment[55,57].

 Diet can also contribute to cancer initiation and progression indirectly by favoring the obesity through over-nutrition and imbalanced diets. Obesity is closely linked to chronic inflammation, a significant cancer risk factor, as previously reported; since adipose tissue, when in a hyperplastic and hypertrophic status, is overloaded with a variety of pro-inflammatory immune cells, including classically activated macrophages, natural killer (NK) cells, mast cells, neutrophils, dendritic cells (DCs), B cells, CTL and T helpers 1 (Th1) cells[58]. These cells release pro-inflammatory factors, such as interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), interleukin 1β (IL-1β), and interleukin 6 (IL-6), which lead to the increase of local and systemic inflammation and insulin resistance[33], becoming a strong promoter of tumor progression[59].

 The presence of insulin resistance cells culminates to hyperinsulinemia and hyperglycemia, two important tumor-promoting effects; in fact, high concentrations of insulin, glucose, and non-esterified fatty acid (NEFA) are strong promoters of cell survival, growth, and proliferation and exert similar effects on tumor progenitors. In addition, high glucose concentrations favor glycolytic cancer cell metabolism characterized by enhanced glucose consumption[33]. Moreover, during obesity the adipose tissue macrophages (ATM), which in healthy conditions are skewed towards the M2 anti- inflammatory phenotype, are directed to pro-inflammatory M1 macrophages[60]. The M1 macrophages produce tumor-promoting cytokines (*e.g.*, TNF, IL-6, and IL-1b) and chemokines, such as Monocyte chemoattractant protein-1 (MCP-1) and Macrophage migration inhibitory factor (MIF)[61].

 These data suggest that the diet modulation could be used as a form of cancer chemoprevention in healthy individuals. In pharmacology, chemoprevention is used to describe the “use of pharmacological or natural agents that inhibits the development of invasive cancer either by blocking the DNA damage that initiates carcinogenesis or by arresting or reversing the progression of pre-malignant cells in which such damage has already occurred”[62].

 Diet is also associated with the modulation of the gut microbiome that has a significant role in host metabolism, nutrition and physiological features (intestinal epithelial cell proliferation and differentiation, pH, function) as well as with the development of the immune system and protection against pathogens[63-65]. But, other than the diet, the GM is influenced by numerous and incompletely elucidated factors, such as host genetics, gender, age, anthropometric parameters, health/disease condition, geographic and socio- economic factors, exhibiting a huge diversity among individuals[66]. In healthy conditions, the GM plays a key role in the maintenance of the host physiological condition, by modulating the host’s immunity. The GM can influence the neutrophil migration and function[67] as well as the differentiation of T cell subsets into Th1, Th2, and Th17 or regulatory T cells (Tregs)[68-70]. By fermenting non-digestible complex carbohydrates such as dietary fiber, these commensal bacteria can produce short-chain fatty acids (SCFAs), which can cross the intestinal epithelium and reach the *lamina propria*, directly shaping the mucosal immune responses[71].

 SCFAs modulate the phenotype and function of numerous immunologically relevant cells, such as colonic epithelial cells, macrophages, neutrophils and DCs[72]. Moreover, upon butyrate (one of the most produced SCAFs) stimulation, the CD4+ effector T cells increase the expression of T-bet and IFN-γ, being able to exert either beneficial or detrimental effects on the mucosal immune system, depending on its concentration and immunological milieu[73]. The presence of CTLs and IFN-γ-producing Th1 cells has been associated with prolonged survival[74,75], making some SCFAs as butyrate, propionate, or acetate being considered as a potential therapeutic tool to modulate inflammatory responses[76,77] including for CRC treatment[78]. Nevertheless, it is important to consider that SCFAs interact with the receptor GPR43 of colonic Tregs, as well as act as histone deacetylase (HDAC) inhibitors on the nucleus of mucosal peripheral Tregs, which in healthy conditions, helps to maintain intestinal immune homeostasis[79-81]. However, in the tumoral scenario (*e.g.*,CRC) it can impair the anti-tumor immunity, decreasing effectors T cells’ proliferation[82].

 The role of the GM in the CRC progression deserves special attention since there is a strong interaction between GM, the intestinal barrier and the immune system’s cells[83-85]. Increased permeability of the epithelial layer, for example, allows the translocation of bacteria, antigens and toxins from the lumen to the *lamina propria* into the blood stream, which may initiate both local and systemic immune responses[86]. These changes can modify inflammatory cell response, requiring them to integrate signals (*e.g.*,cytokines) with cues, such as the local oxygen concentrations and other metabolites, promoting epithelial cells damages that can lead to tumor development[6].

 Clinical, epidemiological and experimental data demonstrated that nutrition and foods have a central role in cancer onset, because it can change the tumor risk, the diagnosis after the onset and the life quality after treatment, other than contribute to ameliorate the adverse effects of chemotherapy and radiotherapy[87,88]. “Functional foods” and “nutraceuticals” are foods or food components that supply health benefits beyond basic nutrition, like peptides and proteins, amino acids, polyunsaturated fatty acids, dietary fibers, oligosaccharides, vitamins, minerals, antioxidants, probiotics and prebiotics, oils and fatty acids, carbohydrates and fibers[89]. In particular, we have focused on the immune-modulating ability of probiotics and prebiotics, which make them a potential adjuvant therapy on anti-CRC treatments.

## ADJUVANT ROLE OF PROBIOTICS AND PREBIOTICS IN CRC TREATMENTS

Probiotics are defined [(by the International Scientific Association for Probiotics and Prebiotics (ISAPP)] as “live microorganisms that, when administered in adequate amounts, confer a health benefit on the host”[90]. They can excerpt health-promoting effects as antimicrobial activities against gut pathogens, decrease blood cholesterol levels, reduce colitis and inflammation, regulate of the host energy metabolism and modulate the immune system[91,92]. In the last years, the use of probiotics and prebiotics to control the onset/progression, or their application as adjuvant therapies in different diseases such as influenza[93], nonalcoholic fatty liver disease[94], pancreatitis[95], Parkinson disease[96] is being deeply investigated. In addition, their use is also being considered as a potential anti-cancer alternative or adjuvant therapy[97], since the pro/pre-biotics can improve the safety of and decrease the side effects of cancer treatment (as demonstrated in a few significant clinical trials)[98-100].

 In addition to the direct role on GM modulation, probiotics present direct anti-cancer effects by the inactivation of carcinogens or mutagens, alteration of cell differentiation and by the production of immunomodulatory effects[101-103]. They increase the immunostimulatory activities, improving gut barrier actions by secreting anti-carcinogenic and anti-oxidative molecules[104,105], and finally activating mononuclear cells, lymphocytes and increasing immunoglobulin A production[106,107]. Probiotics’ administration also reduces the expression of certain Toll like receptors (TLRs), increasing the resistance of the epithelial barrier[102], and activate the phagocytes, which contribute to the maintenance of a vigilance state against tumor cells, especially in the early stages of progression[108].

 The use of the *Lactobacillus rhamnosus* GG (LGG) strain decreased the cellular proliferation and carcinogenesis, since reduces β-catenin and Bcl-2 concentrations and increases p53 and Bax in rats. Moreover, this strain can reduce levels of pro-inflammatory molecules such as COX-2 and NF-κB-p65[103]. But, recently the administrated a mix of *Bifidobacterium spp and Lactobacillus spp* (the two main strains studied as probiotics in CRC therapies)[109], induced the secretion of anti-inflammatory cytokines and up-regulation of gene expression related to Treg and Th2 response[110]. However, we, in agreement and supported by other study, believe that Tregs can play protective roles prior to cancer initiation in “inflammation-prone” cancers but, after the tumor establishment, the Tregs can be co-opted by tumors, assuming a pro-tumorigenic role. In this way, we think that the use of specific probiotics should be applicate to prevent the early phases of CRC[111].

 In CRC, the probiotics’ administration (aiming to modulate the GM and immune response) has been proved a promising innovative approach to counteract CRC progression and increase the chemotherapy effectiveness[112]. In an animal model, the administration of combined *Bifidobacterium longum* and *Bifidobacterium breve* has improved cancer control, strongly reduced tumor development and increased the efficacy of a PD-L1 blocking antibody against cancers[113]. The administration of *Lactobacillus lactis* can reduce the concentration of hydrogen peroxide (H2O2) and the increment of the catalase activity, decreasing tissue inflammation and colonic damage in a BALB/c mouse model. These data suggest that bacteria are capable of affecting mediators of inflammation, such as cytokines[114]. However, the use of some bacterial strains as probiotics could have side effects. The *Lactobacillus acidophilus* induces the mRNA expression of CXCR4 (stromal-derived factor-1 receptor) and reduces the tumor growth by 50% in treated mice and improves the apoptosis of CT-26 cancer cells, showing a role in metastasis prevention; but its administration also suppressed MHC-class I expression, which is crucial in cancer surveillance[115]. Due to the heterogeneous immunomodulatory roles of probiotics, we believe that, to accurate the target in the anti-CRC battle, a specific selection of the bacterial strain is fundamental to have a probiotic effectiveness. The disease stage progression, for example, could be an important determining factor in the probiotic strains choice. Moreover, the probiotics’ use in cancer patients generates concern due to the risk of infection and the transfer of antibiotic resistance. Nevertheless, randomized clinical trials have not reported a significant increase in the risk of adverse effects following probiotic supplementation, when compared to patients who received a placebo, or even have been proven safe and beneficial in these patients[116].

 As an adjuvant therapy, concomitant to chemo/radiotherapy in CRC patients, some clinical assays have proven that probiotics can be an efficacious treatment[117], since the supplementation with *Lactobacillus rhamnosus* decreased the frequency of diarrhea, abdominal distress and dose reductions due to intestinal toxicity, in comparison to patients with placebo[118]. A randomized clinical trial about the efficacy and tolerability of *Lactobacillus rhamnosus* in patients with radiation-induced diarrhea, showed that patients which receive probiotics had better fecal consistency and decreased bowel movements[119].

 Furthermore, since diet is a crucial risk factor in CRC susceptibility[120-122], the administration of prebiotics (that are able to favor specific changes in the composition and/or GM activity), could confer benefits upon the hosts well- being and health[123]. Prebiotics are carbohydrate, principally oligosaccharides, including fructooligossacharides (FOS) xyloogliosaccharides (XOS), inulin, fructans, galactogliosaccharides (GOS)[124,125]. They are able to resist the digestion in the human small intestine and then reach the colon, becoming substrate to fermentation by the GM. Prebiotics’ administration inhibits aberrant crypt formation and SCFAs’ production[126], reduces caecal pH[127] and in addition, it shows anti-carcinogenic impact on the presence of resistant starch, inulin and other oligo-fructans[128,129]. Besides that, the prebiotics show anti-cancer properties by down regulating the expression levels of COX-2, iNOS, NF-kB, and gastrointestinal glutathione peroxidase, by their bifidogenic effects and immunomodulatory roles. Finally, the prebiotics are also able to modulate the GM, inhibit the pathogens’ multiplication and enhance the cell apoptosis[130-134].

 Probiotics work synergistically with prebiotics (symbiotic) to exert a beneficial impact on GM and generally on intestinal health, which make them a potential therapeutic strategy in the CRC. *Lactobacillus* and *Bifidobacteria* combined with prebiotics, such as oligofructose and inulin, showed to counteract tumor progression. A pro/prebiotic cocktail of *Bifidobacterium infantum, Lactobacillus acidophilus*, *Bifidobacterium bifidum*, maltodextrin (LBB) and oligofructose increased intestinal ZO-1, MUC2, TLR2 and occludin, and reduced COX-2 and TLR4 in rats[102].

## CONCLUSION

The manipulation of nutrients could have potential implications for both the prevention as well as the treatment of CRC since it can affect a diverse range of mechanisms, such as cell signaling, apoptosis, and mainly immune system regulation, other than the overlying influence on the gut microbiome.

 Diet has a great ability to modulate the cell responses to environmental stimuli, as well as a balanced nutritional regime can improve the immune metabolism, by enhancing the cytotoxic efficiency of CD8+ TIL within the tumor mass, showing a potential role in improving cancer prognosis. Furthermore, diet can modulate the GM; and since the intestinal immune system is constantly exposed to numerous xenobiotic and endobiotic metabolites (which shape mucosal immune function and inflammation), the intestinal microbiome along with the local immune system maintain the balance between mucosal tolerance and inflammation. In other words, the GM manipulation should be a promising treatment to improve the outcomes in CRC.

 The fine mechanisms by which the dietary nutrients enhance the anti- cancer effects of standard anticancer therapies have not been fully elucidated yet.

 But the actual scenario of poor prognosis for many cancer patients, in addition to the severe documented adverse events of current anti-cancer therapies, suggest the crucial need to find complementary treatments, that have limited patient toxicity and simultaneously enhance therapy responses in cancer versus normal cells. The data discussed in this review seem suggest that the investigation of the probiotic/prebiotic application as coadjutant anti-cancer treatments can give in the future interesting results; however, we believe that it is still necessary to plan different clinical trial in order to confirm these very promising results in humans.

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**Table 1 Summarized the main references used in this review, which pointed diet as a harmful or protective to host health**

|  |  |
| --- | --- |
| **Pathways** | **Ref.** |
| **Harmful** | **Protective** |
| High ratio saturated fat  | [27,34,39,40] |  |
| Obesity and cancer | [3,32,34,40,63] |  |
| Meat intake | [29,39,41-44,123,124] | [32,45] |
| Alcohol intake  | [41] |  |
| Carbohydrates intake | [25,28,58] | [26,73] |
| Host microbiota and cancer | [65,87,100,133] | [70,72,100,105] |
| Probiotics and prebiotics supplementation  |  | [69,93-96,98,99,101,102,104,106,107,110,111,116-119] |



**Figure 1 Diet components can act directly or indirectly on the prevention or initiation/progression of cancer.** Beneficial direct actions are exemplified by nutrients, which can direct protect the cells from DNA damage, and decrease the oxidative stress, while the harmful directly effect could be exemplify by DNA damage, activation of growth signaling proto-oncogenes and changes on proinflammatory cytokines. The indirect beneficial and harmful effects are represented by the modulation of gut microbiota and obesity induction respectively. HCA: Heterocyclic amines; PAH: Polycyclic aromatic hydrocarbon.