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Review article

Possible role of nutrition in the prevention of inflammatory bowel disease–related colorectal cancer: A focus on human studies

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ABSTRACT

Patients with inflammatory bowel disease (IBD) are at substantially high risk for colorectal cancer (CRC). IBD-associated CRC accounts for roughly 10% to 15% of the annual mortality in patients with IBD. IBD-related CRC also affects younger patients compared with sporadic CRC, with a 5-y survival rate of 50%. Regardless of medical therapies, the persistent inflammatory state characterizing IBD raises the risk for precancerous changes and CRC, with additional input from several elements, including genetic and environmental risk factors, IBD-associated comorbidities, intestinal barrier dysfunction, and gut microbiota modifications. It is well known that nutritional habits and dietary bioactive compounds can influence IBD-associated inflammation, microbiome abundance and composition, oxidative stress balance, and gut permeability.

Additionally, in recent years, results from broad epidemiologic and experimental studies have associated certain foods or nutritional patterns with the risk for colorectal neoplasia. The present study aimed to review the possible role of nutrition in preventing IBD-related CRC, focusing specifically on human studies. It emerges that nutritional interventions based on healthy, nutrient-dense dietary patterns characterized by a high intake of fiber, vegetables, fruit, ω-3 polyunsaturated fatty acids, and a low amount of animal proteins, processed foods, and alcohol, combined with probiotic supplementation have the potential of reducing IBD-activity and preventing the risk of IBD-related CRC through different mechanisms, suggesting that targeted nutritional interventions may represent a novel promising approach for the prevention and management of IBD-associated CRC.

Introduction

Inflammatory bowel disease (IBD), comprising Crohn's disease (CD) and ulcerative colitis (UC), are chronic recurrent immune-mediated disorders affecting the gastrointestinal tract. CD and UC are of multifactorial etiology and are characterized by a complex interplay between host genetic susceptibility and environmental factors such as diet, gut microbiota, and infections [1,2]. The

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incidence and prevalence of IBD are constantly rising in several parts of the world, with ~3 million individuals affected by IBD across Europe alone [3,4], highlighting its emergence as a global burden. Patients with IBD are at substantially higher risk (2- to 2.5-fold compared with the general population) of developing colorectal cancer (CRC), also referred to as colitis-associated cancer (CAC) or IBD-related CRC, which accounts for about 10% to 15% of the annual mortality in patients with IBD [5–7]. When a similar colonic extent is affected, the risk for developing CRC is similar between CD and UC patients compared with the general population matching for sex, age, and years at risk [5].

CAC has a more elevated malignancy potential than sporadic CRC, and the typically advanced stage of IBD-related CRC in diagnosis reduces life expectancy [8]. A more significant proportion of two or more synchronous primary neoplasms in CAC and a higher histologic grade and poor survival rate were observed in IBD-associated CRC compared with sporadic CRC [9]. IBD-related CRC affects younger patients compared with sporadic CRC, with a 5-y survival rate of 50% [6]. Population-related studies show that IBD and CRC have a comparable global prevalence with a rising incidence in north-western Europe and the United States. Moreover, both diseases are linked with Westernized behaviors and lifestyles, especially dietary habits [10,11]. Nutritional patterns rich in animal fat and poor in fruit and vegetables can trigger of IBD and cancer [12,13]. Dietary preventive strategies may represent a promising approach considering the correlation between diet and cancer. Previous studies have shown that the risk for CAC increases with several factors, including longer duration of IBD and disease extent, young age at onset, the grade of inflammation, coexistence with primary sclerosing cholangitis (PSC), and other hepatobiliary or metabolic conditions, and familial history of CRC [14]. Table 1 lists the most important known risk factors for developing dysplasia and CRC in patients with IBD. Analogous to sporadic CRC, IBD-related CRC follows consecutive events of genomic mutations. However, despite several common mechanisms, CAC exhibits clinical, genetic, and molecular characteristics different from those of sporadic CRC [15,16]. Intricately interconnected pathways, including immunologic responses via mucosal inflammatory mediators, intestinal microbiota, gut permeability, the gut–liver axis, oxidative stress, and genomic instability, also participate in the pathogenesis of CAC [17,18]. After an analysis of the current knowledge about CAC pathogenesis, in this narrative review, we investigate the possible implications of nutrition as a protective or risk factor for IBD-related CRC by examining the influence of diet, dietary bioactive compounds, and nutritional patterns on genomic stability, oxidative stress, IBD, the modulation of IBD-related inflammation, gut microbiota, intestinal barrier function, as well as specific IBD-associated CRC pathways and risk factors, given the opportunity to ultimately design new preventive strategies.

Table 1
Main risk factors for the development of dysplasia and CRC in patients with IBD

Risk factors	References
Long duration of IBD	[14]
	[19]
	[20]
	[8]
	[21]
Increased extent of colitis (pancolitis) in UC	[20]
	[22]
	[21]
Severity of histologic bowel inflammation	[23]
	[24]
	[25]
	[14]
	[19]
	[22]
Active inflammation	[14]
	[26]
	[8]
	[22]
	[27]
Younger age of IBD onset	[28]
	[19]
	[29]
PSC, NAFLD	[19]
	[30]
	[31]
	[32]
	[33]
MetS, sarcopenic obesity, dyslipidemia	[31]
	[34]
	[35]
	[36]
	[33]
	[37]
Family history of CRC or dysplastic colonic polyps	[24]
	[19]

CRC, colorectal cancer; IBD, inflammatory bowel disease; MetS, metabolic syndrome; NAFLD, non-alcoholic fatty liver disease; PSC, primary sclerosing cholangitis; UC, ulcerative colitis.

Methods

A literature search was carried out using PubMed and diverse combinations of search terms and Boolean operators for each topic (see Supplementary file 1). We considered the following main topics to investigate the possible effects of diet on the most important risk factors or mechanisms of CAC:

- IBD-related CRC;
- Nutrition and CRC, nutrition and IBD-associated CRC;
- Nutrition and IBD, inflammation and oxidative stress;
- Nutrition and genomic instability;
- Nutrition and PSC;
- Nutrition, microbiota, and IBD-related CRC;
- Nutrition and intestinal barrier function; and
- Nutrition, obesity, metabolic syndrome (MetS), non-alcoholic fatty liver disease (NAFLD), and IBD-related CRC.

Only human-focused studies, both in vivo and in vitro, e.g., observational and interventional studies in IBD, IBD-related inflammation or CRC, studies on human cells and tissues, and papers written in English, were reviewed (either abstracts or full text). We identified 4,501,218 publications and included 287 in this narrative review. Table 2 outlines the number of results found, the number of papers considered for each topic, the time the literature search was done, and the number of reviewers.

Results

IBD-associated CRC pathogenesis

Chronic inflammation and reiterate cycles of relapse and remission of disease seem to be the main factors predisposing patients with IBD to the risk for developing IBD-related CRC [38–40]. However, mounting evidence firmly suggests that IBD-associated CRC development is multifactorial. It could be ascribed to concurrent disruption of oxidative balance, intestinal dysbiosis, gut-barrier dysfunction, hepatobiliary, and metabolic conditions, all influenced by genetic and environmental factors, including dietary habits. Although sporadic CRC develops through the adenoma-carcinoma progression with a multistage process, in CAC, the

Table 2
Main topics considered to investigate the possible effect of diet on the most important risk factors or mechanisms of CAC, time in which the literature search was done, number of reviewers, number of results retrieved, and number of papers considered for each topic

Topic	Time of search/No. of reviewers	No. of results retrieved	No. of papers considered
IBD-related CRC	15 March 2022/3	849,851	51
Nutrition and CRC, nutrition and IBD-associated CRC	30 April 2022/3	183,362	16
Nutrition and IBD, inflammation and oxidative stress	29 December 2022/3	1,199,625	63
Nutrition and genomic instability	30 April 2022/3	8130	33
Nutrition and PSC	30 April 2022/3	314	8
Nutrition, microbiota and IBD-related CRC	29 December 2022/3	3088	58
Nutrition and intestinal barrier function	29 December 2022/3	3872	43
Nutrition, obesity, MetS, NAFLD and IBD-related CRC	29 December 2022/3	2367	15
	Overall search time interval: March–December 2022	Total results retrieved 4,501,218	Total papers considered 287

CAC, colitis-associated cancer; CRC, colorectal cancer; IBD, inflammatory bowel disease; MetS, metabolic syndrome; NAFLD, non-alcoholic fatty liver disease; PSC, primary sclerosing cholangitis.

evolution of dysplasia/cancer not always follows a linear trend from low- to high-grade dysplasia to carcinoma. Indeed, CAC may arise in patients without any prior history of dysplasia. Sporadic CRC typically arises from polypoid adenoma, whereas IBD-CRC generally develops from flat dysplasia with indistinct margins (Choi et al. 2017, [41]). Aneuploidy, an indicator of genomic instability, has been found in 20% to 50% of dysplastic lesions and ≤90% of cancers and is found in long-lasting UC ([42–44], Willenbucher et al. 1997). The two main forms of genomic instability observed in sporadic CRC are chromosomal and microsatellite instabilities. Chromosomal and microsatellite instabilities in CAC appear to have a similar frequency (85% chromosomal instability, 15% microsatellite instability) as observed in sporadic CRC. However, they differ in timing and frequency from the pattern seen with sporadic CRC [45]. For example, the loss of the adenomatous polyposis coli (*APC*) tumor suppressor gene appears early during the evolution of sporadic CRC. It is generally a late phenomenon in IBD-cancer progression, if it happens at all. Additionally, p53 mutations occur early in CAC, even before dysplasia, yet p53 mutations appear late in sporadic CRC [18]. This evidence suggests that some distinctive pathways connected with the progression of IBD-related CRC seem to be determined mainly by inflammation-associated damage. The molecular mechanisms through which inflammation supports cancer growth and expansion are still uncovered and may differ between CAC and other forms of CRC [46]. Nuclear factor (NF) k light-chain-enhancer of activated B cells is a crucial regulator of inflammation in IBD and can be triggered by a large group of stimuli, such as proinflammatory cytokines, microbial components lipopolysaccharide (LPS), viruses, and DNA-damaging agents. It has been demonstrated that NF-κB is abnormally activated in 50% of patients with CRC and CAC [47–49]. Several proinflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-1, IL-6, and IL-8 that are encoded by NF-κB pathway's target genes, enhance inflammation-associated tissue damage and are linked to cancer development and progression [50]. Another crucial factor in the pathogenesis of CRC in IBD is the induction of cyclooxygenase (COX)-2, led by inflammatory cues such as TNF-α, IL-1, and interferon (IFN)-γ [51]. COX-2 overexpression was identified in patients with IBD and active inflammation and IBD-associated neoplasia [52]. COX-2 may promote tumor progression by inducing the expression of antiapoptotic proteins that results in resistance to apoptosis. Moreover, overexpression of COX-2 relates to elevated levels of matrix-degrading enzymes and enhanced migration of malignant cells [53,51]. Also, prostaglandin E2 (PGE2), signal transducer and activator of transcription 3 (STAT3), and IL-23/T helper 17 cells (Th17) have been proven to contribute to inflammation in IBD and to promote CAC tumorigenesis [51]. These proinflammatory pathways stimulate the production of growth factors, including vascular endothelial growth factor (VEGF) and chemokines, such as IL-8, to promote angiogenesis, an essential factor for tumor growth and progression [51]. Although the mechanism of intestinal microbiota-induced carcinogenesis remains largely unclear, the gut microbiome has recently emerged as a key factor in the etiopathogenesis of both CRC [54,55] and IBD [56]. In physiologic situations, gut microbiota is a "virtual organ" implicated in indigestible carbohydrates fermentation, short-chain fatty acids (SCFAs) production, vitamin synthesis, gut mucosa integrity, and prevention of pathogenic microorganisms invasion. The equilibrium between proinflammatory and anti-inflammatory cytokines is crucial for gut homeostasis. This equilibrium is influenced by the normal intestinal microbial flora composition, which is affected by several factors, including diet. In addition, specific intestinal microbes have been associated with IBD and CRC [57–59]. Many microbiota-mediated tumorigenic mechanisms have been described, including the modulation of host defenses and inflammatory pathways, oxidative stress induction, bacterial-derived genotoxins, and gut-barrier function [60,61]. Several findings indicate that disruption of the protective intestinal mucosal barrier may play a role in colonic carcinogenesis [62,63]. There is evidence of a gut-barrier breakdown in IBD, although it remains uncertain whether this is a leading contributor to the disease or a result of mucosal inflammation [64]. In CD, the combined effects of TNF-α and IFN-γ cause epithelial injury, which results in tight junction alterations. Disruption of colonic barrier function and augmented intestinal permeability may increase the exposure of colonocytes to toxins from the colonic milieu, promote bacterial products or entire bacteria translocation from the gut lumen to the lamina propria, increasing inflammatory processes, the induction of cytokines, including IL-17, IL-23, and release of reactive oxygen and nitrogen species (RONS) [55,62,65]. RONS can induce DNA damage and interfere with key genes implicated in CAC pathways, such as p53 and DNA mismatch repair genes [66].

Hepatobiliary disorders are frequent extraintestinal manifestations in IBD [67], and ≤30% of patients with IBD have abnormal liver tests [68]. Although the underlying mechanisms remain largely unknown, it has been hypothesized that the gut–liver axis may be involved in CAC and CRC metastasis [32,69,70]. Intestinal inflammation, medications used to control IBD symptoms, gut-barrier disruption, microbiota, and metabolic factors are believed to contribute to the pathogenesis of IBD-associated hepatobiliary diseases and CAC [71–73]. Patients with IBD who are diagnosed with PSC are at higher risk for colorectal dysplasia and cancer [74]. PSC is a persistent cholestatic liver disease characterized by chronic inflammation of the bile ducts and strongly associated with IBD. Although the causal mechanisms of the increased risk of CRC in these patients remain largely unknown, it has been suggested that

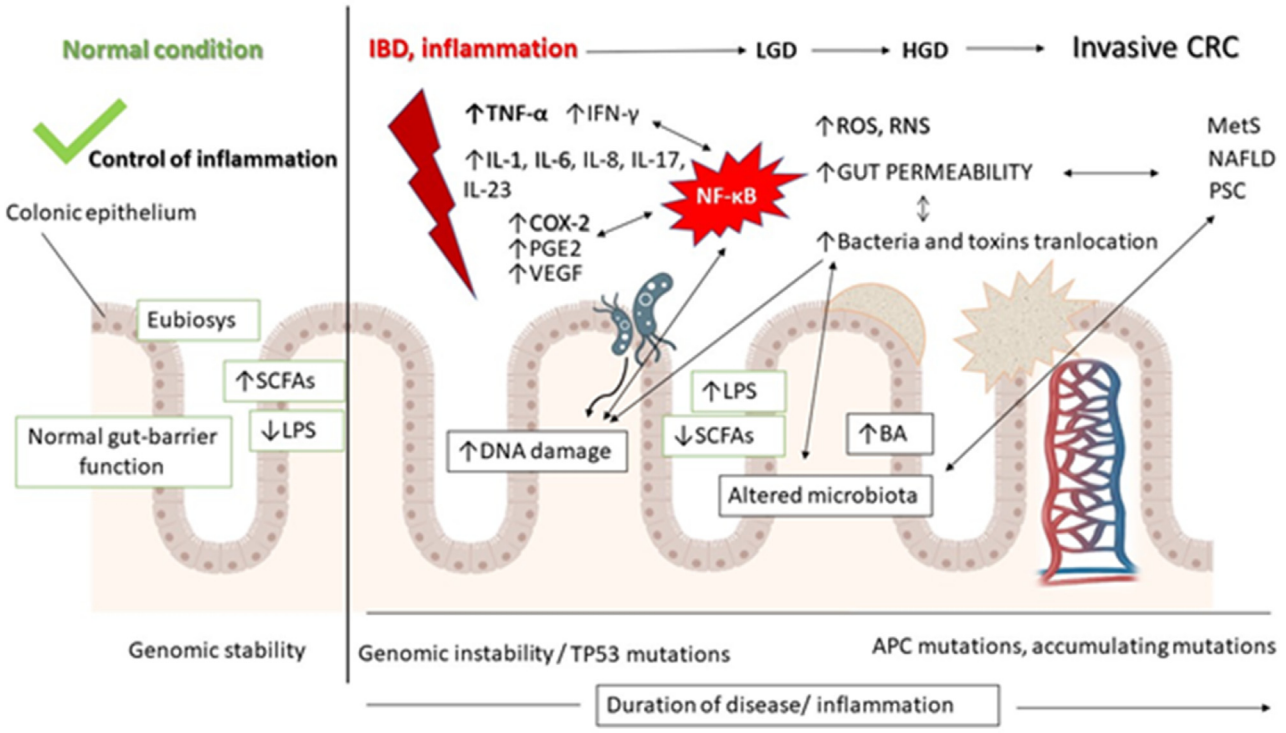

Fig. 1. Key pathogenetic mechanisms in CAC. Normal gut condition is characterized by a balanced microbiota, which produces SCFAs, contributing to gut-barrier integrity, immune homeostasis, and control of inflammation. A healthy intestinal barrier provides nutrient absorption and protection from external factors such as bacteria and toxins, avoiding DNA damage and promoting genomic stability. Chronic inflammation resulting from inflammatory bowel disease can initiate and promote carcinogenesis through the induction of DNA damage, genomic instability and TP53 mutations, caused for example, by exposure to ROS/RNS or to mutagenic compounds owing to epithelial barrier disruption, which in turn may promote microbiota dysbiosis, increasing of LPS and bacterial translocation and thus triggering hepatobiliary conditions linked to CAC. Elevated NF-kB and inflammatory cytokines can also increase VEGF expression, stimulating tumor angiogenesis. Hepatobiliary and metabolic conditions can independently alter the microbiota, and promote inflammation and carcinogenesis. APC, adenomatous polyposis coli, BA, bile acid; CAC, colitis-associated colorectal cancer, COX, cyclooxygenase; CRC, colorectal cancer; HGD, high-grade dysplasia; IFN, interferon; IL, interleukin; LGD, low-grade dysplasia; LPS, lipopolysaccharide; MetS, metabolic syndrome; NAFLD, non-alcoholic fatty liver disease; NF, nuclear factor; PGE2, prostaglandin-E2; PSC, primary sclerosing cholangitis; RNS, reactive nitrogen species; ROS, reactive oxygen species; SCAF, short-chain fatty acid; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

bile acids (BA) may play a key role. PSC characteristically presents compromised hepatic excretion of BAs that may cause secondary BA colonic build-up [75]. It has been hypothesized that BAs may act as carcinogens in human gastrointestinal cancers [76,77]. The high prevalence of colorectal neoplasms in the right proximal colon, where secondary BA concentrations are the highest, suggests BA involvement in carcinogenesis [78,79]. This is corroborated by the evidence that ursodeoxycholic acid reduced the risk for CRC in patients with PSC and IBD by 80% [80] by reducing the colonic concentration of the secondary BA as a carcinogen [81,82].

Recent data reveal that the prevalence of NAFLD among patients with IBD is higher when compared with the general population [83] and that its severity is correlated with the presence of MetS [84]. Moreover, it has been shown that CRC is strongly associated with NAFLD, primarily if NAFLD is associated with MetS [31,33,85]. Figure 1 summarizes the primary factors and signaling pathways involved in CAC pathogenesis, including tumor initiation, promotion, and progression.

IBD-associated CRC and nutrition

Strong evidence continues to show that certain nutritional patterns and dietary components may have a protective or detrimental effect on cancer risk, including CRC in humans ([86–92], D'Avanzo et al. 2022). Indeed, it has been assessed that nutritional factors account for about half of all CRC cases [93]. Consequently nutrition and lifestyle are crucial intervention goals in primary prevention. These nutritional factors may influence several stages of carcinogenesis through diverse interacting mechanisms as they play a role in oxidative stress, genomic instability/stability, angiogenesis, modulation of host defenses and inflammatory pathways, and IBD onset and severity. They may also indirectly influence visceral obesity, metabolic syndrome, and hepatobiliary conditions—known risk factors for IBD complications and/or CRC. Emerging evidence also indicates that the intestinal microbiota and the gut-barrier function are crucial effectors in the association between nutrition, IBD, and cancer [62].

Influence of nutrition on genomic instability

The links between nutrition and genomic instability have been scrutinized for several decades. Evidence indicates a substantial causal or preventive role for different nutritional factors that can influence all relevant genomic stability and crucial tumorigenic pathways, such as exposure to dietary carcinogens, DNA damage and repair, epigenetic modifications, and apoptosis [94–97].

By acting as cofactors or enzyme substrates, micronutrients may protect from DNA damage, promote DNA repair and CpG island methylation, and lead to cell responses, including apoptosis, differentiation, or proliferation, promoting genomic stability [98]. Some micronutrients, including selenium [99,100] and zinc [101], have been widely studied for their crucial roles in cancer prevention [102].

Higher dietary folate (vitamin B9) intake or high plasma folate levels have been linked toreduced risk for CRC initiation risk [103]. Naturally present in foods such as green leafy vegetables, legumes, and citrus fruits, folate acts at the cellular level to maintain genomic stability by providing nucleotides for DNA replication/repair and controlling DNA methylation and gene expression. Folate deficiency may induce uracil misincorporation into DNA, increase DNA strand breakage, inhibit DNA base excision repair capacity and induce DNA hypomethylation and, consequently, aberrant gene and protein expression, leading to carcinogenesis [104,105]. Conversely, some studies indicated that excess folate intake might be detrimental, promoting tumor growth [106]. Besides folic acid and folate, other nutritional factors may similarly affect folate metabolism, particularly alcohol, methionine, and choline. Alcohol antagonizes folate by interfering with its absorption and affecting different stages of folate metabolism, while methionine and choline are among the primary dietary sources of methyl groups in humans. Diets characterized by high consumption of alcohol and low intake of folate and methionine are considered "methyl-poor." In contrast, those lacking in alcohol and high in folate and methionine are "methyl-rich." Research findings on combinations of these nutritional factors have generally observed a higher risk for CRC associated with methyl-poor nutritional patterns than methyl-rich diets, supporting additional evidence for the beneficial role of folate in genome stabilization and CRC prevention [107]. Interestingly, several vitamin and mineral deficiencies, including lower folate levels, have been described in patients with IBD and CRC [108].

Oxidative stress, defined as an imbalance between the production of reactive oxygen/nitrogen species (ROS/RNS) and antioxidant defenses, is a crucial component responsible for DNA damage, genomic instability, and tumorigenesis. Numerous studies have documented the increased expression and detrimental effects of ROS/RNS in human IBD and CRC [109–112]. Interaction between ROS/RNS and DNA is one of carcinogenesis's main contributing factors. Oxidative stress-related damage of DNA methylation patterns results in genomic instability and mutations. For example, oxidative stress-associated DNA disruption of tumor suppressor genes, such as p53 or other key genes involved in carcinogenic pathways, drives UC to CRC [113,114]. A multicenter case–control study of CRC examined the link between p53 mutations and diet and found that patients with p53 mutation were more likely to consume a Western diet than controls. Precise characteristics of this Western diet, including high glycemic load and increased intake of red meat, fast food, and trans-fatty acid, seemed most strongly linked with p53 mutations. These data suggest that some components of a Western-style diet may contribute to a p53-CRC disease pathway [96], possibly by a detrimental influence on genomic stability, as Western diets have been linked with increased oxidative stress and inflammation levels [115]. This may be very important considering that the p53 gene mutation may occur early during IBD and represents a key event in IBD-related dysplasia and CRC initiation [116,117]; Fig. 1). Interestingly, several miRNAs found in human and bovine milk are known suppressors of the p53 gene (*TP53*). The very high homology of bovine and human milk miRNAs sequences, particularly in their seed region central to their function, suggests that ingestion of milk-derived miRNAs may disrupt the complex balance in the level of crucial gene regulatory miRNAs altering gene expression, which promotes pathophysiologic processes such as cancer [118]. A study reported that long-term alcohol intake, particularly consumption of liquor, raises the likelihood of having CRC with microsatellite instability (MSI). The probability of MSI in the tumor from the cumulative effects of high alcohol consumption and smoking cigarettes revealed a 70% excess risk. Some indications showed that elevated refined grain intake might also correlate with MSI-positive cancers, even though associations were less consistent [95]. A substantial relationship was found between the malignant potential of IBD-associated CRC and high MSI [119].

Increased intake of heterocyclic amines (i.e., mutagenic and carcinogenic chemicals formed during high-temperature cooking of muscle meats such as beef, pork, poultry, and fish) have been associated with colon carcinogenesis [120]. Epidemiologic studies [121–125] support a strong association between the ingestion of red meat and increased risk for CRC. Recent research by Gurjao et al. [123] indicates that red meat consumption may cause alkylating damage to DNA, leading to CRC-causing mutations associated with poor survival [123]. Conversely, low-meat and vegetarian diets prevent cancer [126], since fruits and vegetables contain antioxidants, which act as free radical scavengers and prevent DNA damage [127]. Plant-based dietary patterns include various bioactive components linked with decreased cancer risk [89,128]. These components can protect cells by influencing the endogenous antioxidant system and transformation/detoxification pathways [129]. Bioactive compounds such as flavonoids [130], carotenoids [131,132], resveratrol [133], curcumin and silymarin [134], folate (Williams and Jacobson 2010), and total oligomeric flavonoids [135], exhibit both direct actions against tumor cells and antioxidant or anti-inflammatory effects. Several in vitro [136–141] and clinical studies [142–144] demonstrated that strawberry, black raspberry, and their bioactive components have effective protective actions on inflammation, oxidative stress, genomic instability, IBD and CRC, indicating their potential role as dietary interventions in IBD patients for cancer prevention [145,102].

Nutritional factors influencing inflammation and IBD

The most important risk factors for IBD-associated CRC are related to chronic intestinal inflammation and oxidative stress. They include increased extent and/or severity of colitis, long duration of IBD and younger age of disease onset. It has been shown that nutrition plays an essential role as a protective or trigger factor in the development of IBD. It continues to act as a modulator of intestinal inflammation once the disease becomes established [13,146,147]. Moreover, the inflammatory potential of the diet has been associated with an increased risk for CRC [148]. Several nutritional factors or dietary bioactive compounds can interfere with carcinogenesis by regulating IBD-related inflammatory processes or oxidative stress, either directly or indirectly, by modifying the gut microbiota and/or body composition [149,150]. Several epidemiologic, observational, prospective, and retrospective case–control assessments, including a report by the Nutrition Cluster of the International Organization for the Study of Inflammatory Bowel Diseases ([151–154,], Sakamoto et al. 2005,) have been explored the effects of diet on IBD. A frequent finding from comprehensive observational studies is that a Western diet, characterized by high consumption of total fat (specifically animal fats, ω-6 polyunsaturated fatty acids [PUFAs)], dairy fats), refined sugars and grain, animal proteins, meat, especially red meat, and reduced intakes of vegetables and fruit, results in greater risk for developing IBD and/or disease relapses [152,155–158]. A meta-analysis by Ge et al. [159] associated meat consumption with an increased risk for IBD. By contrast, an analysis of data from the FACES (Food and Crohn's Disease Exacerbation Study) trial showed that among CD patients in remission, the consumption of red and processed meat was not related to symptomatic relapse [160]. Lo et al. [161] found dietary patterns with high inflammatory potential to be associated with

increased risk for CD but not UC in an analysis of three large prospective cohorts [161]. A typical hallmark of the Western diet is a high intake of food additives through the consumption of ultra-processed food. An epidemiologic study indicated that the growing incidence of CD might be due to increased food additives intake through processed foods and beverages [162]. For example, it has been shown that emulsifiers increase NF-κB and IL-8 in human intestinal epithelial cells [163] and are associated with inflammation and disease relapse in patients with UC in remission [164]. Some studies suggest that intake of trans-unsaturated fatty acids is associated with an increased incidence of UC [155], CRC, and CRC-metastasis in humans [165,166]. Trans-unsaturated fatty acids are produced during the partial hydrogenation of vegetable oils, oils/fats heating in ultra-processed food, or can occur naturally in ruminant meat and dairy products.

On the other hand, anti-inflammatory dietary patterns focused on non-refined foods and plant-based protein sources may have utility in treating IBD and maintaining of remission [167–169]. Specifically, lacto-ovo vegetarian diet has been shown to be highly effective in preventing relapse of CD in patients who have achieved remission [170] and in reducing the risk for colorectal adenomas [171]. A cross-sectional study of healthy individuals described an inverse correlation between fiber intake and circulating levels of different proinflammatory markers, including IL-1β, IL-6, and TNFα, implicated in IBD and CRC [172]. A clinical trial with patients with UC revealed a decrease in endoscopic index parameters and clinical activity following supplementation with fiber (20–30 g/d of germinated barley; [173]).

Penagini et al. have recently explored the scientific literature on all aspects of nutrition in pediatric IBD. According to their systematic review, nutrition has a substantial role in early-onset IBD and indicated that nutritional patterns characterized by intake of meats, desserts, fatty foods, and high sugar consumption are correlated with an augmented risk for disease in children. They also confirmed that consumption of vegetables, fruits, olive oil, whole meal bread, and fish could be a potential protective factor. It has also been shown that an imbalance in fatty acids, vegetables, and fruits intake is linked with increased risk for CD in children [174]. Scoditti et al. [175] have demonstrated that olive oil and red wine polyphenols decrease inflammatory angiogenesis in human cultured endothelial cells, through inhibition of COX-2, matrix-degrading proteases expression and prostanoid production, suggesting a potential protective role for dietary polyphenols in inflammation and cancer. However, despite molecular evidence pointing to the intestinal microvascular angiogenesis or remodeling as a phenomenon involved in the promotion and persistence of IBD-related inflammation (Pousa, Maté, and Gisbert 2008), it should be considered that most of the inflammation in IBD takes place in the lumen rather than in the endothelium. Tursi et al. discussed the progression to diverticulitis in patients with diverticulosis, tackling luminal intestinal inflammation and its remedies. The authors reported that a predominantly vegetarian diet (that is naturally rich in polyphenols) and low in red meat may be beneficial in reducing intestinal inflammation [150], suggesting a role for polyphenols in counteracting inflammation both at endothelial and luminal level.

It has been demonstrated that PUFA supplementation decreases inflammatory cytokines and inflammation and protects against the development of IBD [176–178]. The Mediterranean diet is rich in fruits, vegetables, whole grains, legumes, nuts, and olive oil. It is characterized by moderate intakes of fish, dairy products, and red wine and a very low consumption of saturated fat, meat, and sweets. This dietary pattern ensures nutrients such as essential fatty acids, vitamin D, minerals, and fiber. It is particularly rich in natural bioactive compounds, namely extra-nutritive components found in small amounts in foods, ensuring beneficial effects on health beyond the fundamental nutritional value. These dietary bioactive compounds, including alkaloids, polyphenols, flavonoids, terpenoids, sterols, pigments, and PUFAs of ω-3 series, found mainly in plant-derived food, nuts, and seeds can interact with key factors and modulate the pathways implicated in inflammation cascades associated with IBD and tumorigenesis. The Mediterranean diet reduces inflammation and to be a protective factor against some diseases, including IBD and CRC [179,180]. Koloverou et al. [181] reported that reduced C-reactive protein, fibrinogen, TNF-α, and IL-6 levels were correlated with high adherence to the Mediterranean diet over a 10-y period. The given health advantages of the Mediterranean diet could be supported by the modulating effect on genes linked to inflammation and oxidative stress, including TNF-α and IFN-γ genes [182].

Fasting, caloric restriction, and caloric restriction mimetics (for foods or compounds that simulate the biological effects of caloric restriction, including marine-derived carotenoid-rich foods, sweet potatoes, resveratrol, turmeric, spermidine, hydroxy-citrate), and other gentler fasting approaches have been associated with a plethora of beneficial health effects including reduction of systemic inflammation and anticancer effects, as well as a decrease in the tumorigenic and metastatic potential of cancer stem cells, which are commonly considered responsible of cancer development and relapse [183]. Although fasting-mimicking diet has been shown to reduce intestinal inflammation, promote colonic regeneration, and reverse intestinal pathology in mouse models of IBD [184], no data on patients with IBD is yet available. Alcohol consumption has been shown to promote intestinal inflammation, affecting disease onset and recurrence. Additionally, alcohol use may interfere with several drug metabolism, resulting in increased adverse effects or even loss of effectiveness, which in turn may lead to inflammation and colitis exacerbation (White, Ramos, and Kane 2021).

These findings demonstrate how adequate dietary habits are essential in supporting drug therapy and reducing IBD-associated inflammation as a possible strategy to reduce the risk for IBD-related CRC.

Influence of nutrition on gut microbiota in relation to IBD and CRC

Any variation in the gut microbiota composition and abundance that can disrupt microbial homeostasis (i.e., dysbiosis correlates with intestinal inflammation; [185]) and several gut pathologies, including IBD and CRC [56,186,187]. Nutrition is among the most critical factors influencing the gut microbiota composition and abundance. The intestinal microbiota uses ingested nutrients as an energy supply in fundamental biological processes, and modifications in a dietary pattern or consumption of specific food-derived components may change the composition of the gut microbiota; as species best adapted to metabolize specific food components will grow, whereas other species may become less abundant. These changes in the abundance and composition of the intestinal microbiota may affect host physiology by influencing several biological processes, including inflammatory/anti-inflammatory balance, metabolic homeostasis, immune function, and intestinal permeability. Prebiotics and fibers are dietary components that support beneficial intestinal colonization by microbes and/or microbial release of anti-inflammatory metabolites. Calder et al. [149] reviewed the details of studies in which prebiotics or fiber have been investigated for their effects on human inflammatory markers. The authors have shown that these interventions consistently lowered the concentrations of several inflammatory markers and particularly C-reactive protein, demonstrating that it is highly

plausible that microbiota modulation by prebiotic fiber reduces inflammation [149].

The reduction of bacteria with anti-inflammatory properties and the expansion of bacteria with inflammatory capabilities are observed in IBD patients in comparison to healthy individuals [188,189].

A study by Machiels et al. found that SCFA-producing bacteria are less abundant in patients with IBD, which may result in long-lasting intestinal inflammation responses connected with colitis-associated CRC. The most important SCFAs generated by indigestible dietary plant-fiber fermentation are acetate, butyrate, and propionate, which have been shown to beneficially affect the host via different mechanisms, including the modulation of inflammation in IBD, promotion of colonic mucosa regeneration, apoptosis, and differentiation of colonic cancer cells [190–193].

Butyrate and acetate help to regulate mucus production and discharge, thus protecting the intestinal mucosa. Decreased mucus secretion/enhanced bacterial catabolism and fermentation of amino acids may augment potentially harmful proinflammatory and carcinogenic metabolites such as ammonia, amines, branched-chain fatty acids, and n-nitroso complex components (Biswas et al. 2022). According to these findings, dietary patterns particularly rich in fiber such as plant-based or semi-vegetarian diets, have been associated with a lower risk of IBD and CRC onset and progression [156,194–197]. Results from studies indicate that modulating diet with prebiotic and probiotic foods/supplements to promote the selection and expansion of fiber-fermenting microbiota may help decrease IBD inflammation and risk for CRC [198–200]. It has been shown that treatment with probiotics (e.g., *Lactobacillus* spp) benefits both colitis and associated PSC. These results indicate that the microbiota and intestinal inflammation are closely associated with the pathogenesis of IBD-related PSC. Thus control of gut inflammation and preservation of microbial homeostasis via dietary manipulation may be important for treating both IBD and PSC, potentially preventing CRC [201]. Caloric restriction has been associated with *Lactobacillus* and *Bifidobacterium* expansion that has been linked with a reduction in body weight, total cholesterol levels, and triacylglycerols, as well as with a reduction of bacterial strains associated with mucosa inflammation. Additionally, intermittent fasting has been proven to change microbiota composition by increasing SCFA-producing bacteria [183]. Although certain microbial genera, such as*Lactobacillus* and *Bifidobacterium*, may reduce the inflammatory response in the gut by decreasing the expression of proinflammatory cytokines and promoting the generation of anti-inflammatory ones [185], specific intestinal bacteria have been recently associated both with inflammation during IBD, and CRC. Increasing evidence suggests that the oral/intestinal commensal bacterium *Fusobacterium nucleatum* is linked with gut immune disease, including UC. The amount of *F. nucleatum* has been positively associated with the disease activity in UC [202]. It has also been shown that *F. nucleatum* is significantly enriched in the feces of patients with IBD, and its abundance is correlated with clinical disease activity [59]. Furthermore, accumulating data support the potentially crucial role of *F. nucleatum* colorectal colonization in CRC development [58]. Although the role of *F. nucleatum* in the mediation of the connection between nutrition and the risk for CRC is still unknown, a population-based study showed that diets that may induce intestinal inflammation, such as foods rich in red and processed meat, are related to increased risk for *F. nucleatum*-positive CRC, but not carcinomas that do not contain these bacteria [203]. An analysis by Mehta et al. [204] showed that prudent diets rich in whole grains and dietary fiber are associated with a lower risk for *F. nucleatum*-positive CRC but not *F. nucleatum*-negative cancer. Furthermore, an integrated analysis using meta-transcriptomics and epidemiologic data showed a correlation between alcohol consumption and the abundance of *Fusobacterium* in CRC tissue, suggesting a potential link between alcohol metabolism and subsequent carcinogenesis caused by *F. nucleatum* [205]. Prolonged and/or excessive intake of alcohol is a critical risk factor for several cancers, including CRC [206]. Additionally, it has been shown that chronic alcohol consumption is a potential trigger for flare in IBD [207]. The metabolism of the microbiota may play a role in the toxicity of alcohol, particularly in the gastrointestinal tract, where ethanol is converted in acetaldehyde by aerobic and facultative anaerobic bacteria. Indeed, acetaldehyde is highly toxic, prooxidant, proinflammatory, and procarcinogenic, with several detrimental effects associated with colorectal carcinogeneses, such as DNA damage, impaired DNA excision repair, and folate degradation [206,208]. Colonization by *Streptococcus gallolyticus* (also known as *S. Bovis* type 1) has been associated both with IBD and CRC, although there are some studies on the role of this bacterium in the etiopathogenesis of gastrointestinal diseases, including IBD and CRC [209–211]. Several in vitro studies indicated that *S. bovis/gallolyticus* proteins trigger inflammatory cytokine production, resulting in the production of pro-carcinogenic ROS and RNS and promoting angiogenesis [212]. Although the nutritional factors leading to *S. bovis/gallolyticus* successful colonization are largely unknown, some studies suggest that the consumption of red meat and raw milk products (particularly from dairy cows with mastitis) may result in the transmission of *S. bovis/gallolyticus* between animals and humans, since the bacterium has been detected in such foods [213]. Trimethylamine N-oxide (TMAO) is a microbiota-derived metabolite associated with several disorders/diseases, including IBD, PSC, MetS, NAFLD, and CRC [214–218]. Intestinal anaerobes produce TMAO through the digestion of dietary carnitine and choline, mainly found in foods of animal origin, especially red meat, with lower amounts found in fish and beans. Vegetarians show a different intestinal microbiota makeup than omnivores, with a decreased capacity to generate TMAO precursors. TMAO plasma concentrations appear comparable in lacto-ovo-vegetarians and vegans [200,219,220]. It has been shown that adherence to the Mediterranean diet, particularly rich in fruits and vegetables, may result in decreased TMAO levels [220,221].

Gut microbiota is vital to maintain sufficient vitamin levels in the human body, which are crucial to support gut homeostasis and prevent carcinogenesis. Folate, riboflavin, and cobalamin (i.e., vitamins B_9, B_2, and B_{12}), produced in large quantities by gut microbiota, are essential for DNA synthesis, methylation, repair, and stability. Folate has received the most investigation as a CRC preventive agent [180,200,222]. A metabolomic analysis by De Filippis et al. [221] showed enrichment of folate biosynthesis in people following a Mediterranean or vegan diet compared with omnivores. Vegetable-rich dietary patterns have been also associated with increased microbiota biodiversity and abundance [223]. This may be particularly important considering that mucosa-associated gut bacteria in patients with IBD-related CRC seem to be featured by an overall reduction in biodiversity [224]. Recent studies have shown that high consumption of refined sugars may shift the balance of microbiota, resulting in enhanced pro-inflammatory properties, and reduced colonic epithelial integrity and mucosal immunity, which can promote low-grade systemic inflammation and metabolic endotoxemia [225]. According to these findings, high sugar intake has been associated with the exacerbation of inflammation in IBD and CRC [226–228]. These findings support the potential role of gut microbiota in mediating the link between diet, IBD, and CRC, suggesting that nutritional interventions might

be employed in precision medicine and cancer prevention in patients with IBD.

Nutritional factors influencing gut-barrier function

A reduction in gut-barrier function is supposed to play a crucial role in the pathogenesis of several diseases, including IBD and CRC, as it may promote the passage of harmful factors such as whole bacteria, peptidoglycan, LPS, and other toxins through the barrier, resulting in intestine damage, enhancing inflammatory processes and release of ROS [55,62,64,65]. Moreover, these bacteria or toxins may enter portal circulation, promoting PSC [229] and NAFLD [230], recognized risk factors for CRC in patients with IBD. Diet is an important modulator of gut-barrier function, directly affecting intestinal epithelial cell junctions and consequently modulating permeability or indirectly influencing the microbiota [62,231,232]. The effects of diet components on intestinal barrier function have been recently reviewed, focusing predominantly on human in vivo studies. Researchers reported that dietary fiber, glutamine, probiotic supplementation, and vitamin D enhance barrier integrity, whereas dietary gluten, surfactants, and alcohol decrease gut barrier function. Particularly, dietary SCFAs from resistant starch, nondigestible oligosaccharides, and proteins help to preserve gut-barrier function [233], and it has been demonstrated that increased butyrate production may support the gastrointestinal epithelial lining by increasing expression of tight junctions (TJ) proteins (Bach Knudsen et al. 2018). Excessive alcohol intake has been shown to alter the gut-barrier and increase intestinal permeability, directly and indirectly promoting immune activation and inflammation in IBD (White, Ramos, and Kane 2021, [234]). ω-3 and ω-6 PUFAs upregulate the expression of occludin, a TJ-protein, strengthen the epithelial barrier, and reduce gut permeability [235,236]. It has also been shown that PUFAs can reverse TJ disruption caused by proinflammatory cytokines in Caco 2 intestinal cells [237–239]. Thus, dietary patterns rich in ω-3 and ω-6 PUFAs may have a role in preventing epithelial barrier alterations caused by inflammation or proinflammatory cytokines and, consequently, prevent CRC in patients with IBD. Several studies employing human intestinal epithelial cell lines showed that dietary emulsifiers promote bacterial translocation and inflammation via epithelial TJ disruption [163,240–244]. Additionally, evidence continues to show that dietary emulsifiers such as carrageenan may be implicated in IBD inflammatory processes and, thus, in the development of CAC [164,245,246]. Also, endogenous surfactants such as BAs, typically recognized for their roles in enabling the digestion and absorption of dietary lipids, may disrupt TJ proteins and thus increase gut permeability [232]. Dysregulation of claudins (TJ proteins) relates to augmented intestinal permeability, the perpetuation of inflammation, epithelial to mesenchymal transition, and tumor progression in IBD and subsequent CAC [247]. It has been suggested that claudins may act as signaling proteins and participate in cell differentiation, proliferation, and carcinogenesis through cellular signaling pathways [248]. Some studies suggested a beneficial role for whey proteins in diseases characterized by intestinal barrier dysfunction (including IBD), partly, by modulating claudin expression [249]. It has also been shown that quercetin, a common flavonoid found in fruits, vegetables, and grains, increases epithelial resistance in Caco-2 cell monolayers via upregulation of claudin 4 expression [250]. Some human studies are starting to confirm the beneficial effects of dietary polyphenols (including flavonoids) on intestinal barrier function and microbiota homeostasis [251,252]. In this regard, Del Bo et al. have shown, for the first time, that a polyphenol-rich diet can reduce serum zonulin levels, an indirect marker of intestinal permeability [].

According to recent studies, *Akkermansia muciniphila*, a mucin-degrading bacterial intestinal microorganism, has important regulatory effects on gut homeostasis and barrier function, acting as a "seal" rather than a mere probiotic [253]. In in vitro human cell line models, Caco-2 and HT-29, *A. muciniphila* was found to improve enterocyte monolayer integrity and increase the expression of cell–cell adhesion and TJ molecules [254,255], suggesting that *A. muciniphila* may increase the integrity of the intestinal barrier. Not surprisingly, lower colonization and abundance of *A. muciniphila* were observed in patients with IBD [256]. This organism seems to be sensitive to specific dietary factors [257], and human studies showed that fermentable oligo-, di- and monosaccharides and polyols (which includes fructose, lactose, oligosaccharides, and sugar alcohols; FODMAP) the content in diet might significantly increase *A. muciniphila* abundance, possibly improving gut–barrier function [258,259].

These findings may represent a foundation for possible dietary treatments for the management of intestinal permeability, inflammation, and gut function in patients with IBD, with the ultimate goal of preventing CAC.

Obesity, MetS, hepatobiliary comorbidities, and CRC

Although IBD was previously believed to be a condition characterized by undernourishment and low body mass index (BMI), cumulative evidence shows that IBD does not strictly result in hyponutrition but frequently leads to malnutrition, with an increased risk for overweight or obesity in both adults and children with IBD (Long et al. 2011, [260]). Visceral fat and related risk for MetS has been linked with complicated and more severe disease courses and increased rate of relapses in CD, thus suggesting that adipose tissue might exacerbate inflammation in IBD [261]. Obesity has been associated with a weak response to pharmacologic therapies in CD and UC and with CRC risk [261,262]. Holtmann et al. [263] have also demonstrated better results after pharmacologic treatment in patients with UC with BMI kept <25 kg/m^2, indicating the benefit of body weight control in patients with IBD through dietary interventions. Additionally, obesity can lead to NAFLD, a condition frequently found in patients with IBD [83]. Visceral obesity, dyslipidemia, MetS, and NAFLD-related liver failure can promote CAC and CRC liver metastasis [31–33,35,85]. Notably, high-fat diets increase secondary BAs buildup, a known risk factor for colonic inflammation and CRC, especially in patients with PSC IBD, whose hepatic excretion of BA is impaired [75]. BA can produce ROS and RNS, resulting in DNA damage, mutation, and genomic instability in colonocytes [78]. Although nutritional therapy has not been strictly explored in PSC, Suskind et al. [264] suggest that diet may play a critical role in the control and prevention of PSC in patients with IBD, possibly influencing the risk for CAC. They reported a case of clinical remission and normalization of laboratory parameters in a patient with UC and PSC using dietary therapy based on a specific carbohydrate diet, which restricts complex carbohydrates from grains and eliminates refined sugar.

In addition to obesity, MetS, and hepatobiliary conditions, malnutrition and micronutrient deficiencies are risk factors for IBD severity and complications (Russell et al. 2021), including CAC neoplasia. It has been shown that vitamin D deficiency is associated with poor outcomes in patients with IBD and risk for CRC [265,266]. In contrast, low red blood cell folate correlates with an enhanced risk for dysplasia and CRC in patients with UC [267]. Moreover, imbalances in the ratio of copper to zinc have been associated with colon carcinogenesis [268].

Chicco et al. [269] examined the effects of the Mediterranean dietary pattern on the nutritional state, liver steatosis, clinical

disease activity, and quality of life of patients with IBD, including those with NAFLD. Chicco et al. observed a substantial lowering of malnutrition-associated parameters and liver steatosis in patients with CD and UC after a short-term nutritional intervention based adopting the Mediterranean diet. A spontaneous amelioration in inflammatory markers and disease activity accompanied this. Cytokines secreted by adipose tissue or related to obesity, such as TNF-α and IL-6 play a pivotal role in the chronic state of low-grade systemic inflammation associated with CRC initiation and progression [270]. Low-fat diets have been demonstrated to decrease plasmatic levels of NF-κB–regulated inflammatory cytokines and vascular endothelial growth factor [149,271].

Discussion

The incidence and prevalence of IBD are increasing worldwide. Despite many therapeutic options, currently available pharmacologic therapies for IBD treatment have demonstrated only partial effects on CRC chemoprevention. Their long-term systemic toxicity has restricted their clinical application for this purpose [272,145]. Additionally, diagnosing precancerous neoplasia in IBD often is challenging because of the contextual inflammation and the unavailability of sensitive biomarkers [9]. For these reasons, dietary-based approaches are essential not only to control IBD-associated symptoms but also because they may offer substantial cancer prevention effects through the modulation of several factors connected to colon carcinogenesis, including oxidative stress, DNA damage and genomic instability, gut–liver axis, intestinal microbiota, gut-barrier function, nutritional status, and body composition.

Based on the main risk factors and key pathogenetic mechanisms associated with CRC in patients with IBD, we have reviewed the possible role of nutrition and dietary bioactive compounds on IBD CRC and on the following:

- Genomic instability/stability;
- IBD, inflammation, and oxidative stress;
- PSC;
- Microbiota and IBD, microbiota and IBD-related CRC;
- Intestinal barrier function in IBD and CRC; and
- Obesity, MetS, NAFLD, and IBD-related CRC.

Several micronutrients, such as selenium and zinc; vitamins (e.g., folic acid); and dietary bioactive compounds (e.g., flavonoids, carotenoids, resveratrol, silymarin) show a beneficial effect, protecting from DNA damage, promoting DNA repair, regulating cell apoptosis, differentiation, or proliferation, and counteracting oxidative stress, thus promoting genomic stability. On the other hand, high alcohol consumption and specific microbiota metabolites such as TMAO and n-nitroso compounds, mainly resulting from red and processed meat metabolism, promote genomic instability, oxidative stress, inflammation, worsening of hepatobiliary conditions such as PSC, NAFLD, and cancer.

Vitamin D, ω-3-PUFAs, and SCFAs produced by anaerobic fermentation of dietary fibers demonstrate favorable influences on the modulation of inflammatory processes, microbiota composition, gut-barrier, and immune and metabolic function, potentially influencing IBD and CAC. Conversely, animal-derived fats, trans-unsaturated fatty acids, micronutrients, and vitamin deficiency/imbalance (e.g., copper and zinc) can induce a proinflammatory effects, disrupting intestinal microbiota and barrier function, thus possibly promoting IBD and cancer.

Figure 2 shows the most important nutritional factors influencing the complex network underlying IBD-related CRC pathogenesis.

Overall, it emerges that nutritional habits that emphasize nutrient density via intake of fruits and vegetables (rich in beneficial fiber and bioactive compounds such as antioxidants and polyphenols), healthy fats (e.g., ω-3 PUFAs, olive oil), low amounts of

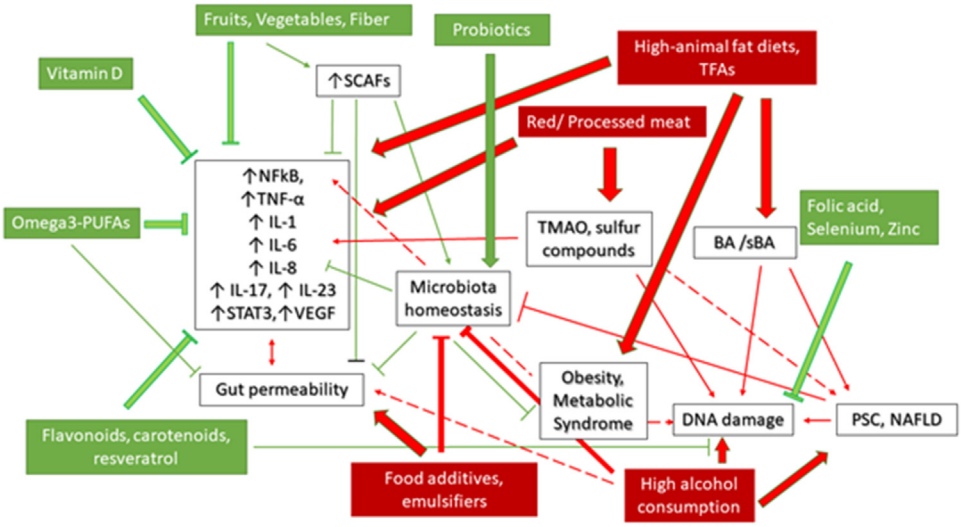

Fig. 2. Schematic representation of the most important nutritional factors influencing the complex network underlying inflammatory bowel disease-related CRC pathogenesis. Imbalanced, Western-like, high-animal fat diets elicit deregulation of inflammatory cytokines, and promote obesity and metabolic syndrome. Red and processed meat consumption increases TMAO and sulfur compounds that lead to DNA damage and inflammation. Western dietary patterns are rich in food additives that disrupt microbiota homeostasis and increase gut permeability. Chronic alcohol consumption may cause DNA damage via microbiota-derived metabolites and may exacerbate hepatobiliary conditions such as PSC and NAFLD. Fruits, vegetables, and fiber inhibit inflammation directly by modulating inflammatory cytokines or indirectly by increasing SCFA production and promoting microbiota homeostasis and reinforcing gut barrier. Vitamin D, ω-3 PUFAs, and plant-derived bioactive compounds such as flavonoids, carotenoids, and resveratrol downregulate proinflammatory cytokines and/or enhance intestinal barrier function. Flavonoids, carotenoids, and resveratrol also act as antioxidants protecting cells from DNA damage, resulting in an anticancer activity. Micronutrients such as folic acid, selenium, and zinc have a role in DNA repair processes. Probiotic supplementation helps maintain microbiota homeostasis and preserve intestinal barrier function. BA, bile acid; IL, interleukin; NAFLD, non-alcoholic fatty liver disease; PSC, primary sclerosing cholangitis; PUFA, polyunsaturated fatty acid; sBA, secondary bile acid; SCAF, short-chain fatty acid; TFA, trans-fatty acid; TMAO, trimethylamine N-oxide; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

animal proteins, raw and whole foods (rather than refined ones) using fresh ingredients rather than prepackaged foods, and probiotic supplementation, may be beneficial to prevent gut inflammation and CAC. Cleaner dietary patterns also allow one to avoid an overabundance of calories, minimizing intake of emulsifiers, refined sugars, and other artificial components characteristic of the Western diet linked to several disease conditions, including IBD and CAC. Unfortunately, patients with IBD tend to consume substantially more animal protein, refined cereals, simple carbohydrates/sugars, dietary fat, and cholesterol, thus avoiding fiber in an attempt to alleviate their symptoms. Adoption of these nutritional habits in the long-term may influence vital cellular elements of the colonic tissue, causing a significant level of inflammation, oxidative stress, DNA damage, and genomic instability, and likely influencing the development of colitis-associated CRC [90,273,274]. Moreover, many clinicians recommend that patients with IBD avoid or consume small amounts of fiber from fruits and vegetables. However, there is no substantial evidence to support the benefit of this intervention [147,275].

Although general dietary recommendations and generic health behavior can help prevent CRC in patients with IBD, there is no such thing as a perfect diet for everyone. For example, fiber, which is generally beneficial, often is reported as intolerable by some patients with IBD (unfermented β-fructan). It has been hypothesized that fiber remains intact in selected patients with decreased fiber fermenting gut microbes and can bind host cell receptors, subsequently enhancing intestinal inflammation [276].

Personalized nutrition at the individual or small group level holds great potential over traditional one-size-fits-all approaches for preventing and treating diet-related diseases, including IBD and CAC [277].

However, further research is needed to improve the understanding of the complex pathways through which diet and nutrition can influence CAC pathogenesis in humans. Novel methods such as next-generation sequencing, high-throughput techniques, machine-learning, and multi-omic approaches, including proteomics, metabolomics, and metagenomics, represent expanding and promising tools to study the influence of dietary factors on health in human biology-based and more physiologically relevant settings [278,279]. This lays the foundations for future personalized nutritional approaches preventing CRC in patients with IBD, taking into account individual characteristics, including genetic risk factors, specific inflammatory biomarkers, hepatobiliary and metabolic comorbidities, and microbiota composition.

Conclusions

Nutritional interventions based on healthy, nutrient-dense dietary patterns characterized by a high intake of fiber, vegetables, fruit, ω-3 PUFAs, and low in animal proteins, processed foods, and alcohol, combined with probiotic supplementation, have the potential of reducing IBD activity and preventing the risk for IBD-related CRC through several mechanisms including the modulation of gut inflammation, oxidative stress, genomic instability, microbiota homeostasis, intestinal permeability, gut–liver axis, and metabolic assets. It would be essential to stress how good dietary patterns are fundamental in assisting drug therapy and reducing IBD-associated symptoms as a potential strategy to reduce the risk for IBD-related CRC. Targeted nutritional interventions that consider individual risk factors, hepatobiliary and metabolic comorbidities, genetic characteristics, and microbiota composition may represent a novel promising approach to preventing and managing IBD-associated CRC.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.nut.2023.111980.

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