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Possible role of nutrition in the prevention of Inflammatory Bowel Disease-related colorectal cancer: a focus on human studies

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Highlights

- Inflammatory bowel disease (IBD) patients have high risk of colorectal cancer (CRC)

- IBD-associated CRC has a greater malignant potential if compared with sporadic CRC
- IBD pharmacologic therapy treatment has partial effects on cancer chemoprevention
- Nutritional factors affect many mechanisms and pathways associated with IBD and CRC
- High intake of fiber, vegetables, Omega-3 PUFAs may prevent IBD-related CRC

Abstract

Inflammatory bowel disease (IBD) patients are at substantially higher risk of colorectal cancer (CRC) and IBD-associated CRC accounts for roughly 10-15% of the annual mortality in IBD patients. IBD-related CRC also affects younger patients if compared with sporadic CRC, with a 5-year survival rate of 50%. Regardless of medical therapies, the persistent inflammation 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 disfunction, 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. In addition, in the last years, results from broad epidemiological and experimental studies have associated certain foods or nutritional patterns with the risk of colorectal neoplasia. Here we review the possible role of nutrition in the prevention of IBD-related CRC, focusing specifically on human studies. In conclusion it emerges that nutritional interventions based on healthy, nutrient-dense dietary patterns characterized by a high intake of fiber, vegetables, fruit, Omega-3 PUFAs, and 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.

Keywords: diet, colitis-associated cancer, CAC, CRC, IBD-colorectal cancer

1.Background

Inflammatory Bowel Disease (IBD), comprising Crohn's disease (CD) and ulcerative colitis (UC), are chronic recurrent immune-mediated disorders affecting the gastrointestinal tract. Both diseases 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 (Zhang and Li 2014, Shah and Itzkowitz 2022). The incidence and prevalence of IBD are constantly rising in several parts of the world, with approximately 3 million persons affected by IBD across Europe alone (Burisch et al. 2013, Alatab et al. 2020), highlighting its emergence as a global burden. IBD patients are at substantially higher risk (2-to-2.5-fold compared with the general population) of colorectal cancer (CRC) also referred to colitis-associated cancer (CAC) or IBD-related CRC, which accounts for about 10-15% of the annual mortality in IBD patients (Keller et al. 2019, Giuffrida et al. 2021, Vetter et al. 2021). When similar colonic extent is affected, the risk of developing CRC is similar between CD and UC patients when compared with the general population matching for sex, age, and years at risk (Giuffrida et al. 2021).

CAC has a more elevated malignant potential than sporadic CRC, and the typically advanced stage of IBD-related CRC in diagnosis reduces life expectancy (Romano et al. 2016). There is a greater proportion of two or more synchronous primary neoplasms in CAC and it was observed a higher histologic grade and poor survival rate in IBD-associated CRC than sporadic

CRC (Watanabe et al. 2011). IBD-related CRC affects younger patients if compared with sporadic CRC, with a 5-year survival rate of 50% (Keller et al. 2019). Population-related studies show that IBD and CRC globally have a comparable prevalence with a rising incidence in north-western Europe and the USA. Moreover, both diseases are linked with westernized behaviours and lifestyle, especially with regard to dietary habits (Favoriti et al. 2016, Hnatyszyn et al. 2019). Nutritional patterns rich in animal fat and poor in fruit and vegetables can be crucial triggers of both IBD and cancer (Lewis and Abreu 2017, Khalili et al. 2018). Considering the correlation between diet and cancer, dietary preventive strategies may represent a promising approach. Previous studies have shown that the risk of CAC increases with several factors including longer duration of IBD and disease extent, young age onset, the grade of inflammation, coexistence with primary sclerosing cholangitis (PSC), and other hepatobiliary or metabolic conditions, and familial history of CRC (Kameyama et al. 2018). The most important known risk factors for the development of dysplasia and CRC in IBD patients are listed in table1. 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 (Pekow et al. 2019, Robles et al. 2016). Intricate interconnected pathways, including immunological 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 (Lucafò et al. 2021, Xie and Itzkowitz 2008). After an analysis of the current knowledge about CAC pathogenesis, in this narrative review we investigate the possible implications of nutrition as 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, in view of the opportunity to ultimately design new preventive strategies.

Table 1. Main risk factors for the development of dysplasia and colorectal cancer in patients with inflammatory bowel disease

Risk factors	**References**
Long duration of inflammatory bowel disease	(Kameyama et al. 2018, Beaugerie and Itzkowitz 2015, Karvellas et al. 2007, Romano et al. 2016, Biancone et al. 2012)
Increased extent of colitis (pancolitis) in UC	(Karvellas et al. 2007, Fantini and Guadagni 2021, Biancone et al. 2012)
Severity of histologic bowel inflammation	(Zisman and Rubin 2008, Velayos et al. 2006, Askling et al. 2001, Kameyama et al. 2018, Beaugerie and Itzkowitz 2015, Fantini and Guadagni 2021)
Active inflammation	(Kameyama et al. 2018, Zhao et al. 2015, Romano et al. 2016, Fantini and Guadagni 2021, Santos and Barbosa 2017)
Younger age of IBD onset	(Olén et al. 2020, Beaugerie and Itzkowitz 2015, El-Matary et al. 2020)
PSC, NAFLD	(Beaugerie and Itzkowitz 2015, Fumery et al. 2017, Gleeson and Anderson 2017, Lv, Patel, and Zhang 2019, Pan et al. 2017)
MetS, sarcopenic obesity, dyslipidaemia	(Gleeson and Anderson 2017, Jurjus et al. 2016, Chen et al. 2021, Harlid, Myte, and Van Guelpen 2017, Pan et al. 2017, Yorulmaz et al. 2011)
Family history of colorectal cancer or dysplastic colonic polyps	(Velayos et al. 2006, Beaugerie and Itzkowitz 2015)

Abbreviations: IBD: Inflammatory Bowel Disease; MetS: Metabolic Syndrome; NAFLD: Nonalcoholic Fatty Liver Disease; PSC: primary sclerosing cholangitis; UC: Ulcerative Colitis.

2. Methods

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: 1.IBD-related CRC, 2.Nutrition and CRC, nutrition and IBD-associated CRC, 3.Nutrition and IBD, inflammation and oxidative stress, 4.Nutrition and genomic instability, 5.Nutrition and primary sclerosing cholangitis (PSC), 6.Nutrition, microbiota and IBD-related CRC, 7.Nutrition and intestinal barrier function, and 7.Nutrition, obesity, metabolic syndrome, 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). In total we identified 4.501.218 publications and included 287 in this narrative review. The number of results found and the number of papers considered for each topic, time in which the literature search has been done and the number of reviewers, are outlined in table 2.

Table 2. Main topics considered to investigate the possible effect of diet on the most important risk factors or mechanisms of colitis-associated cancer, time in which the literature search has been 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**
Inflammatory Bowel Disease (IBD)-related colorectal cancer (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	8.130	33
Nutrition and primary sclerosing cholangitis (PSC)	30 April 2022/ 3	314	8
Nutrition, microbiota and IBD-related CRC	29 December 2022 /3	3.088	58
Nutrition and intestinal barrier function	29 December 2022/ 3	3.872	43

Nutrition, obesity, metabolic syndrome, NAFLD and IBD-related CRC	29 December 2022 /3	2.367	15
	Overall search time interval: March-December 2022	Total results retrieved 4.501.218	Total papers considered 287

3. Results

3.1 Inflammatory bowel disease-associated colorectal cancer pathogenesis

Chronic inflammation and reiterate cycles of relapse and remission of disease seem to be the main factors that predispose IBD-patients to the risk of developing IBD-related CRC (Grivennikov 2013, Kim and Chang 2014, Scarpa et al. 2014). However, mounting evidence firmly suggests that IBD-associated CRC development is multifactorial, and it could be ascribed to concurrent disruption of oxidative balance, intestinal dysbiosis, gut-barrier dysfunction, hepatobiliary and metabolic conditions, all of which are influenced both by genetic and environmental factors, including dietary habits.

While sporadic CRC develops through the adenoma-carcinoma progression with a multi-stage process, in CAC, evolution of dysplasia/cancer not always follows a linear trend from low grade dysplasia 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 while IBD-CRC generally develops from flat dysplasia with indistinct margins (Choi et al. 2017, Foersch and Neurath 2014). Aneuploidy, an indicator of genomic instability, has been found in 20-50% of dysplastic lesions and up to 90% of cancers and it is found in long-lasting UC (Kulaylat and Dayton 2010, Triantafillidis, Nasioulas, and Kosmidis 2009, Befrits et al. 1994, Willenbucher et al. 1997). The two main forms of genomic instability observed in sporadic CRC are chromosomal instability and microsatellite instability. Chromosomal and microsatellite instabilities in CAC seem to appear

with a similar frequency (85% chromosomal instability, 15% microsatellite instability) as observed in sporadic CRC, but they differ in the timing and frequency from the pattern seen with sporadic CRC (Cisyk et al. 2018). For example, the loss of Adenomatous Polyposis Coli (APC) tumor suppressor gene appears early during the evolution of sporadic CRC, while it is generally a late phenomenon in IBD-cancer progression if it happens at all. Additionally, p53 mutations occur as an early phenomenon in CAC, even before dysplasia, yet p53 mutations appear late in sporadic CRC (Xie and Itzkowitz 2008). This evidence suggests that there are some distinctive pathways connected with the progression of IBD-related CRC, that seems to be determined mainly by inflammation-associated damage. The molecular mechanisms through which inflammation supports cancer growth and expansion are still being uncovered and may differ between CAC and other forms of CRC (Terzić et al. 2010). Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) is a crucial regulator of inflammation in IBD and can be triggered by a large group of stimuli, such as proinflammatory cytokines, microbial components including lipopolysaccharide (LPS), viruses, and DNA-damaging agents. Particularly, it has been demonstrated that NF-κB is abnormally activated in 50% of patients with CRC and CAC (Kojima et al. 2004, Wang et al. 2009, Karin and Greten 2005). Several proinflammatory cytokines such as tumor necrosis factor (TNF)-α, IL-1, and IL-6, and IL-8 that are encoded by NF-κB pathway's target genes, enhance inflammation-associated tissue damage and are linked with cancer development and progression (Viennois, Chen, and Merlin 2013). 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 IFN-γ (Luo and Zhang 2017). COX-2 overexpression was identified in IBD patients with active inflammation and in IBD-associated neoplasia (Agoff et al. 2000). COX-2 may promote tumor progression by inducing the expression of antiapoptotic proteins that results in resistance to apoptosis. Moreover, overexpression of COX-2 is connected with elevated levels of matrix-degrading enzymes and enhanced migration of malignant cells (Gupta and DuBois 2001, Luo and Zhang 2017). Also

prostaglandin E2 (PGE2), signal transducer and activator of transcription 3 (STAT3), and IL-23/T helper 17 cell (Th17), have been proven both to contribute to inflammation in IBD and to promote CAC tumorigenesis (Luo and Zhang 2017). 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 (Luo and Zhang 2017). Although the mechanism of intestinal microbiota-induced carcinogenesis remains largely unclear, recently, the gut microbiome has emerged as a key factor in the etiopathogenesis of both CRC (Gagnière et al. 2016, Montalban-Arques and Scharl 2019) and IBD (Nishida et al. 2018). In physiological situations, gut microbiota serves as a "virtual organ" implicated in indigestible carbohydrates fermentation, short-chain fatty acids (SCFAs) production, vitamins synthesis, gut mucosa integrity, and prevention of pathogenic microorganisms invasion. The equilibrium between pro-inflammatory and anti-inflammatory cytokines is crucial for gut homeostasis. This equilibrium is influenced by the normal intestinal microbial flora composition, which in turn is affected by several factors, including diet. In addition, specific intestinal microbes have been associated with IBD and CRC (Chamorro et al. 2021, Janati et al. 2020, Liu et al. 2020). Many microbiota-mediated tumorigenic mechanisms have been described, including the modulation of host defences and inflammatory pathways, oxidative stress induction, bacterial derived genotoxins, and gut barrier function (Brennan and Garrett 2016, Cheng, Ling, and Li 2020). Several findings indicate that disruption of the protective intestinal mucosal barrier may play a role in colonic carcinogenesis (Mullin et al. 2000, Genua et al. 2021). There is evidence of gut barrier breakdown in IBD, while it remains uncertain whether this is a leading contributor to disease or a result of mucosal inflammation (Shin and Kim 2018). In CD, the combined effects of TNF-α and Interferon-gamma (IFNγ) causes epithelial injury, that results in tight junctions 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) (Genua et al. 2021, McGuckin et al. 2009, Montalban-Arques and Scharl 2019). RONS can induce DNA damage and interfere with key genes implicated in CAC pathways such as p53 and DNA mismatch repair genes (Kraus and Arber 2009).

Hepatobiliary disorders are frequent extra-intestinal manifestations in IBD (Silva et al. 2019), and up to 30% of patients with IBD have abnormal liver tests (Mendes et al. 2007). Although the underlying mechanisms remain largely unknown, it has been hypothesized that the gut-liver axis may be involved in CAC and CRC metastasis (Lv, Patel, and Zhang 2019, Eksteen 2016, Wang and Leong 2014). 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 (Bessissow et al. 2016, Magrì et al. 2019, Verdugo-Meza et al. 2020). IBD patients diagnosed with primary sclerosing cholangitis (PSC) are at higher risk of colorectal dysplasia and cancer (Guerra et al. 2019). 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 increased risk of CRC in these patients remain largely unknown, it has been suggested that bile acids may play a key role. PSC characteristically present compromised hepatic excretion of bile acids, that may cause secondary bile acids colonic build-up (Torres et al. 2011). It has been hypothesized that bile acids may act as carcinogens in human gastrointestinal cancers (Nguyen et al. 2018, Ajouz, Mukherji, and Shamseddine 2014). The observed high prevalence of colorectal neoplasms in the right proximal colon, where secondary bile acid concentrations are the highest, suggests bile acid involvement in carcinogenesis (Bernstein et al. 2005, Claessen et al. 2009). This is corroborated by the evidence that ursodeoxycholic acid reduced the risk of CRC in PSC patients with IBD by 80% (Tung et al. 2001) by reducing the colonic concentration of the secondary bile acid as a carcinogen (Sjöqvist et al. 2004, Pardi et al.

2003). Moreover, it has been shown that CRC is strongly associated with nonalcoholic fatty liver disease (NAFLD), especially if NAFLD is associated with metabolic syndrome (Gleeson and Anderson 2017, Lin et al. 2014, Pan et al. 2017). Recent data reveal that the prevalence of NAFLD among IBD patients is higher if compared with the general population (Saroli Palumbo et al. 2019) and that its severity is correlated with the presence of metabolic syndrome (Carr et al. 2017).

Main factors and signaling pathways involved CAC pathogenesis including tumor initiation, promotion and progression are summarized in Figure 1.

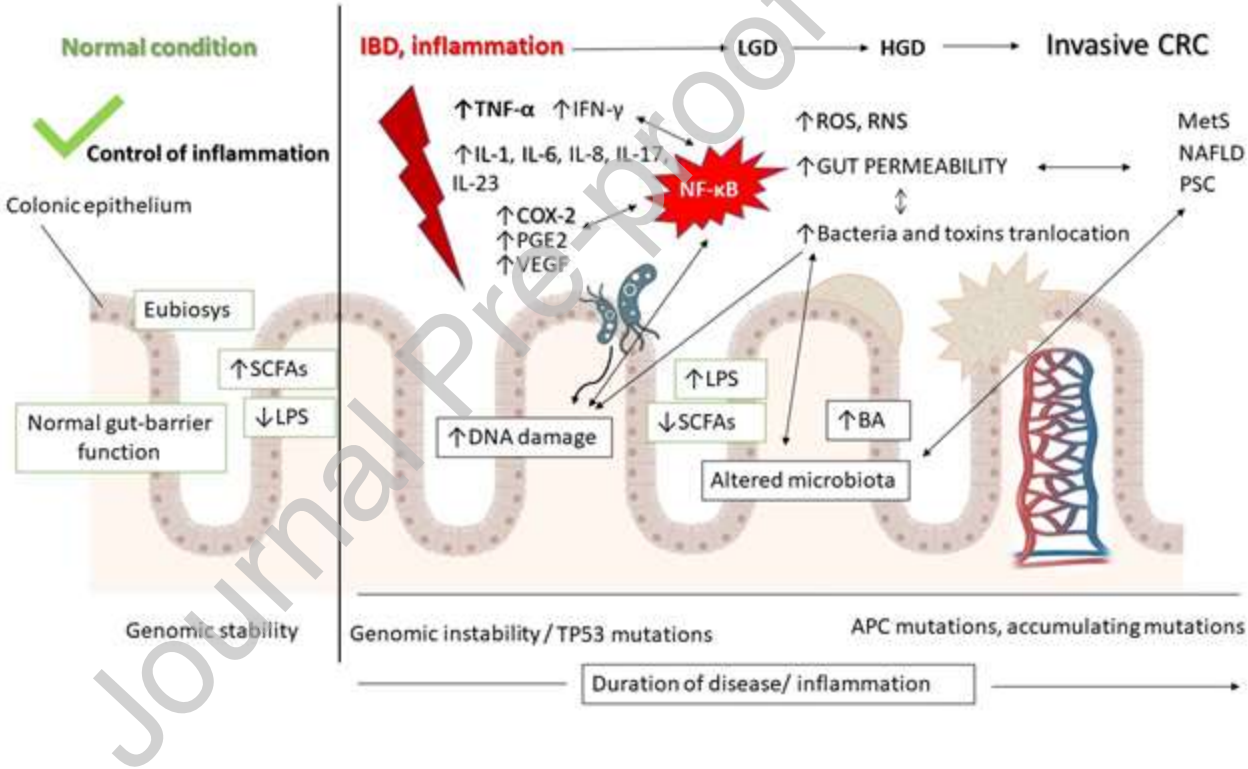

Figure 1. Key pathogenetic mechanisms in colitis-associated colorectal cancer. Normal gut condition is characterized by a balanced microbiota, which produces SCFAs, contributing to gut-barrier integrity, immune homeostasis and control of inflammation. A healthy intestinal barrier provides nutrient absorption and protection from external factors such as bacteria and toxins, avoiding DNA damage and promoting genomic stability. Chronic inflammation resulting from IBD can initiate and promote carcinogenesis through the induction of DNA damage, genomic instability and TP53 mutations, caused for eg. 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 NFkB and inflammatory cytokines can also increase VEGF expression,

stimulating tumor angiogenesis. Hepatobiliary and metabolic conditions can independently alter the microbiota, promote inflammation and carcinogenesis. Abbreviations: BA, Bile Acids; COX-2, Cyclooxygenase-2; HGD, High-grade Dysplasia;IFN-γ, Interferon- γ; IL, Interleuchn; LGD, Low-grade Dysplasia; LPS, Lipopolysaccharide; MetS, Metabolic Syndrome; NAFLD, Non Alcoholic Fatty Liver Disease; PGE2, Prostaglandin-E2; PSC, Primary Sclerosing Cholangitis; RNS, Reactive Nitrogen Species; ROS, Reactive Oxigen Species; SCAFs, Short-Chain Fatty Acids; TNF-α, Tumor Necrosis Factor α ; VEGF, Vascular Endothelial Growth Factor.

3.2 Inflammatory bowel disease-associated colorectal cancer and nutrition

Strong evidences continue to show that certain nutritional patterns and dietary components may have a protective or detrimental effect on cancer risk, including CRC in humans (Thanikachalam and Khan 2019, Veettil et al. 2021, Capurso 2019, Azzeh et al. 2017, Rosman-Urbach et al. 2006, Grosso, Bella, et al. 2017, Franchi et al. 2022, D'Avanzo et al. 2022). Indeed, it has been assessed that nutritional factors account for about half of total CRC cases (Hou, Huo, and Dignam 2013), and consequently nutrition and lifestyle are crucial intervention goals in primary prevention. These nutritional factors may influence several stages of carcinogenesis through diverse interacting mechanisms, since they play a role in oxidative stress, genomic instability/stability, angiogenesis, modulation of host defences and inflammatory pathways, as well as IBD-onset and severity. They may also act indirectly by influencing visceral obesity, metabolic syndrome, and hepatobiliary conditions – which are known risk factors for IBD complications and/or CRC.

3.3 Influence of nutrition on genomic instability

The links between nutrition and genomic instability have been scrutinized for several decades, and 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 (Young 2007, Slattery et al. 2002, Slattery et al. 2001, Ferguson et al. 2015).

Micronutrients, by acting as co-factors or enzyme-substrates, may protect from DNA damage, promote DNA repair and CpG island-methylation as well as they may lead to cell responses including apoptosis, differentiation or proliferation, promoting genomic stability (Ray 2014). Some micronutrients, including selenium (Jayaprakash and Marshall 2011, Lener et al. 2013) and zinc (Ho 2004), have been widely studied for their crucial roles in cancer prevention (Irrazabal et al. 2021).

Higher dietary folate (vitamin B9) intake or high plasma folate levels have been linked with a reduced risk of CRC initiation (Sanjoaquin et al. 2005). Folate, naturally present in foods such as green leafy vegetables, legumes, and citrus fruits, acts at cellular level to maintain genomic stability by providing nucleotides for DNA replication/repair and through the control of DNA methylation and gene expression. Folate deficiency may induce misincorporation of uracil into DNA, increase DNA strand breakage, inhibit DNA base excision repair capacity as well as it may induce DNA hypomethylation and consequently aberrant gene and protein expression, leading to carcinogenesis (Duthie 2011, Catala et al. 2019). Conversely, some studies indicated that an excess of folate intake might be detrimental, promoting tumor growth (Arasaradnam 2010). Of note, apart from 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 by affecting other stages of folate metabolism, while methionine and choline are among the major 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” while those low 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 to “methyl-poor” nutritional patterns compared with “methyl-rich” diets, supporting additional evidence for a beneficial role of folate in genome stabilization and CRC prevention (Giovannucci 2002). Interestingly, several vitamin and mineral deficiencies, including lower levels of folate, have been

described in both IBD and CRC patients (Hwang, Ross, and Mahadevan 2012). Oxidative stress, defined as an imbalance between production of reactive oxygen/nitrogen species (ROS/RNS), and antioxidant defences, is a key 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 (Piechota-Polanczyk and Fichna 2014, Seril et al. 2003, van der Waals et al. 2018, Wang et al. 2016). Interaction between the ROS/RNS and DNA is one the main contributing factors influencing carcinogenesis. 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 (Solomon et al. 2010, Huang et al. 2009). A multicenter case-control study of CRC has examined the link between p53 mutations and diet and found that cases with p53 mutation were more likely to consume a Western-diet compared with controls. Precise characteristics of this Western-diet, including high glycaemic load and increased intake of red meat, fast food, and trans-fatty acid seemed to be 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 (Slattery et al. 2002) possibly by a detrimental influence on genomic stability, since Western diets have been linked with increased oxidative stress and inflammation levels (Aleksandrova, Koelman, and Rodrigues 2021). This may be very important considering that p53 gene mutation may occur early in the course of IBD and represents a key event in IBD-related dysplasia and CRC initiation (Du et al. 2017, Al Bakir, Curtius, and Graham 2018) (see Fig. 1). Interestingly, several miRNAs found in human and bovine milk are known suppressors of 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, that promotes pathophysiological processes such as cancer (Melnik 2017). A study

reported that long-term alcohol intake, particularly consumption of liquor, rise the likelihood of having CRC with microsatellite instability (MSI). The probability of MSI occurrence in the tumor from the cumulative effects of high alcohol consumption and smoking cigarettes revealed a 70% excess in risk. There were some indications that elevated intakes of refined grain might also be correlated with MSI-positive cancers, even though associations were less consistent (Slattery et al. 2001). Notably, a substantial relationship was found between the malignant potential of IBD-associated CRC and high-microsatellite instability (Fujiwara et al. 2008).

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 (Butler et al. 2003). Epidemiological studies (Gurjao et al. 2021, Takachi et al. 2011, Xu et al. 2013, Fu et al. 2011, Cross et al. 2010) continue to support a strong association between the ingestion of red meat and increased risk for CRC. A recent research by Gurjao et al. (2021) indicates that red meat consumption may cause alkylating damage to DNA, leading to CRC-causing mutations that are associated with poor survival (Gurjao et al. 2021). Conversely, low-meat and vegetarian diets seem to prevent cancer (McEvoy, Temple, and Woodside 2012), since fruits and vegetables contain antioxidants, which act as free radical-scavengers and prevent DNA damage (Møller and Loft 2006). Plant-based dietary patterns also consist of a variety of bioactive components linked with decreased cancer risk (Vanamala 2017, Grosso, Godos, et al. 2017). These components can protect cells by influencing the endogenous antioxidant system and transformation/detoxification pathways (Collins, Azqueta, and Langie 2012). Bioactive compounds such as flavonoids (Batra and Sharma 2013), carotenoids (Astley et al. 2002, Mueller and Boehm 2011), resveratrol (Gatz et al. 2008), curcumin and silymarin (Niture et al. 2007), folate (Williams and Jacobson 2010), and total oligomeric flavonoids (Bouhlel et al. 2008), exhibit both direct action against tumor cells and antioxidant or anti-inflammatory effects. Several *in vitro* (Seeram et al. 2006, Wang et al. 2013, Wu et al. 2007, Cho et al. 2015, McDougall

et al. 2008, Zhang et al. 2008) and clinical studies (Wang et al. 2011, Mentor-Marcel et al. 2012, Pan et al. 2015) demonstrated that strawberry, black raspberry and their bioactive components have an 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 (Chen, Shi, and Afzali 2019, Irrazabal et al. 2021).

3.4 Nutritional factors influencing inflammation and Inflammatory Bowel Disease

The most important risk factors for IBD-associated CRC are related to chronic intestinal inflammation and oxidative stress and include increased extent and/or severity of colitis, long duration of IBD, as well as younger age of disease onset. It has been shown that nutrition plays an important role as protective or trigger factor in development of IBD and continues to act as a modulator of intestinal inflammation once disease becomes established (Owczarek et al. 2016, Lewis and Abreu 2017, Kakodkar and Mutlu 2017). Moreover, the inflammatory potential of the diet has been associated with increased risk of CRC (Shivappa et al. 2017). Several nutritional factors or dietary bioactive compounds can interfere with the process of carcinogenesis by regulating IBD-related inflammatory processes or oxidative stress, either directly or indirectly by modifying the gut microbiota and/or body composition (Tursi et al. 2020, Calder et al. 2017). The impact of diet on IBD has been explored in 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 (Shoda et al. 1996, Maconi et al. 2010, Racine et al. 2016, Sakamoto et al. 2005, Levine et al. 2020). A frequent finding from wide observational studies is that a Western diet, characterized by high consumption of total fat (specifically animal fats, n-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 of developing IBD and/or disease relapses (Hou, Abraham, and El-Serag

2011, Racine et al. 2016, Ananthakrishnan et al. 2013, Ananthakrishnan et al. 2014, Jantchou et al. 2010). A meta-analysis by Ge et al. (2015)(Ge et al. 2015) associated meat consumption with an increased risk for IBD. By contrast, an analysis of data from the Food and Crohn's Disease Exacerbation Study (FACES) trial, showed that among CD patients in remission, consumption of red and processed meat was not related to symptomatic relapse (Albenberg et al. 2019). Lo et al. (2020) found dietary patterns with high inflammatory potential to be associated with increased risk of CD but not UC in an analysis of 3 large prospective cohorts (Lo et al. 2020). A typical hallmark of the Western diet is high intake of food additives, through the consumption of ultra-processed food. Noteworthy, an epidemiologic study indicated that the growing incidence of CD may be due to increased food additives intake through processed foods and beverages (Roberts et al. 2013). For example, emulsifiers have been shown to increase NF-κB and IL-8 in human intestinal epithelial cells (Choi et al. 2012) and have been associated with inflammation and disease relapse in patients with UC in remission (Bhattacharyya et al. 2017). Some studies suggests that trans-unsaturated fatty acids intake is associated with an increased incidence of UC (Ananthakrishnan et al. 2014), CRC, and CRC-metastasis in humans (Vinikoor et al. 2010, Ohmori et al. 2017). 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 sources of protein may have utility in both the treatment of IBD and the maintenance of remission (Shivappa et al. 2016, Grosse et al. 2020, Chiba, Ishii, and Komatsu 2019). Specifically, lacto-ovo vegetarian diet has been shown to be highly effective in preventing relapse of CD in patients who have achieved remission (Chiba et al. 2010) and in reducing the risk of colorectal adenomas (Godos et al. 2016). A cross-sectional study of healthy subjects described an inverse correlation between fiber intake and circulating levels of different pro-inflammatory markers, including IL-1β, IL-6, and TNFα, implicated in both IBD and CRC (Chuang et al. 2011). A clinical trial with UC patients revealed a

decrease in endoscopic index parameters and clinical activity following supplementation with fiber (20-30 g/day of germinated barley) (Kanauchi et al. 2002).

Penagini et al. (Penagini et al. 2016) 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, wholemeal bread and fish could be a potential protective factor. It has also been shown that an imbalance in fatty acids, vegetables, and fruits intakes is linked with increased risk for CD in children (Amre et al. 2007). Scoditti et al. (2012) (Scoditti et al. 2012) 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 points to the intestinal microvascular angiogenesis or remodelling as a phenomenon involved in the promotion and persistence of IBD-related inflammation (Pousa, Maté, and Gisbert 2008), it should be taken into account 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 (Tursi et al. 2020), suggesting a role for polyphenols in counteracting inflammation both at endothelial and luminal level.

PUFAs supplementation have been shown to decrease inflammatory cytokines, inflammation, and protect against development of IBD (Stenson et al. 1992, Almallah et al. 2000, Ramirez-Ramirez et al. 2013).

The Mediterranean dietary pattern is particularly rich in fruits, vegetables, whole grains, legumes, nuts, olive oil, and is characterized by a moderate intake of fish, dairy products, 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, fiber, and it is also particularly rich in natural bioactive compounds, namely extra-nutritive components that are found in small amounts in foods ensuring beneficial impact on health beyond the fundamental nutritional value. These dietary bioactive compounds, including alkaloids, polyphenols, flavonoids, terpenoids, sterols, pigments, and PUFAs of omega-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. Mediterranean diet (MD) was shown to reduce inflammation and to be a protective factor for some diseases, including IBD and CRC (Song, Garrett, and Chan 2015, Reddavide et al. 2018). Koloverou et al. (2016) (Koloverou et al. 2016) reported reduced C-reactive protein, fibrinogen, TNFα, and IL-6 levels were correlated with high adherence to MD over a 10 year period. The given health advantages of MD could be supported by the modulating effect on genes linked to inflammation and oxidative stress, including TNF-α and IFNγ genes (Konstantinidou et al. 2013). Fasting, caloric restriction and caloric restriction mimetics (for e.g. foods or compounds that simulate the biological impacts 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 anti-cancer effects, as well as decrease in the tumorigenic and metastatic potential of cancer stem cells, which are commonly considered responsible of cancer development and relapse (Pistollato et al. 2021). Although fasting-mimicking diet has been shown to reduce intestinal inflammation, promote colonic regeneration, and reverse intestinal pathology in mice models of IBD, (Rangan et al. 2019) no data on IBD-patients are available yet. Alcohol consumption has been shown to promote intestinal inflammation and

therefore impact disease onset and recurrence. In addition, alcohol use may interfere with several medications 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).

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

3.5 Influence of nutrition on gut microbiota in relation to inflammatory bowel disease and colorectal cancer

Any variation in the gut microbiota composition and abundance that can disrupt the microbial homeostasis, i.e. dysbiosis, is correlated with intestinal inflammation (Lobionda et al. 2019), and several gut pathologies including IBD and CRC (Nishida et al. 2018, Zou, Fang, and Lee 2018, Gubatan et al. 2022). Nutrition is among the most important factors that can influence the gut microbiota composition and abundance. The intestinal microbiota utilizes ingested nutrients as energy supply in basic biological processes, and modifications in dietary pattern or consumption of specific food-derived components may change the composition of the gut microbiota, as species best adapted to metabolize certain food components will grow, while 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 fibres are best described as dietary components that support beneficial intestinal colonization by microbes and/or microbial release of anti-inflammatory metabolites. Calder et al. (2017) reviewed the details of studies in which prebiotics or fibres have been investigated for their effects on inflammatory markers in humans. The authors have shown that these interventions consistently lowered the concentrations of several inflammatory markers and particularly CRP,

demonstrating that it is highly plausible that microbiota modulation by prebiotic fibres reduces inflammation (Calder et al. 2017).

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 (Frank et al. 2007, Peterson et al. 2008).

A study by Machiels et al. (2014) (Machiels et al. 2014) found that short-chain-fatty-acids (SCFAs) producing bacteria are less abundant in IBD patients, which may result in long-lasting intestinal inflammation response connected with colitis-associated CRC. The most important SCFAs generated by indigestible dietary plant-fiber fermentation are acetate, butyrate, and propionate, that have been shown to beneficially impact the host via different mechanisms, including the modulation of inflammation in IBD, promotion of colonic mucosa regeneration, apoptosis, and differentiation of colonic cancer cells (Carretta et al. 2021, Sokol et al. 2008, Armstrong et al. 2018, Luceri et al. 2016).

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 result in an augment of potentially harmful pro-inflammatory 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 (Pituch-Zdanowska, Banaszkiewicz, and Albrecht 2015, Fritsch et al. 2021, Chiba et al. 2015, Song et al. 2018, Ananthakrishnan et al. 2013). Results from researches performed so far indicate that modulating diet by prebiotic and probiotic foods/supplements to promote the selection and expansion of fiber-fermenting microbiota may help in decreasing IBD inflammation and CRC risk (Tomova et al. 2019, Mack 2011, Jadhav et al. 2020). It has been shown that treatment with probiotics (for eg. *Lactobacillus spp*) provide benefits both for colitis and

associated primary sclerosing cholangitis (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, with the potential to prevent CRC (Shimizu et al. 2012). Caloric restriction has been associated with Lactobacillus and Bifidobacterium expansion that has been linked with a reduction in body weight, total cholesterol levels, and triglycerides as well as with a reduction of bacterial strains associated with mucosa inflammation. In addition intermittent fasting has been proven to change microbiota composition by increasing SCFAs-producing bacteria (Pistollato et al. 2021). While certain microbial genera, such as *Lactobacillus* and *Bifidobacterium*, may reduce the inflammatory response in the gut by decreasing the expression of pro-inflammatory cytokines and promoting the generation of anti-inflammatory ones (Lobionda et al. 2019), specific intestinal bacteria has been recently associated both with inflammation in the course of IBD, and CRC. In particular, there is increasing evidence suggesting that the oral/intestinal commensal bacterium *Fusobacterium nucleatum* is linked with gut immune disease including UC. *F. nucleatum* amount has been positively associated with the disease activity in UC (Su et al. 2020). It has also been shown that *F. nucleatum* is significantly enriched in the feces of patients with IBD and its abundance correlated with disease clinical activity.(Liu et al. 2020) Furthemore, accumulating data support a potentially crucial role of *F. nucleatum* colorectal colonization in CRC development (Janati et al. 2020). Although the role of *F. nucleatum* in the mediation of the connection between nutrition and the risk of 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 of *F. nucleatum*-positive CRC, but not carcinomas that do not contain these bacteria (Liu et al. 2018). An analysis by Mehta et al. (2017) (Mehta et al. 2017) 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 epidemiological 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* (Kim et al. 2020). Prolonged and/or excessive intake of alcohol has been found to be a critical risk factor for several cancers, including CRC (Seitz and Stickel 2007). In addition, it has been shown that chronic alcohol consumption is a potential trigger for flare in IBD (Swanson et al. 2010). Microbiota's metabolism 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, pro-oxidant, pro-inflammatory and pro-carcinogenic, with several detrimental effects that have been associated with colorectal carcinogenesis, such as DNA damage, impaired DNA excision repair, and folate degradation (Na and Lee 2017, Seitz and Stickel 2007). Colonization by *Streptococcus gallolyticus* (known also *as S. Bovis* type 1) has been associated both with IBD and CRC, while there are some evidences on the role of this bacterium in the etiopathogenesis of gastrointestinal diseases, including IBD and CRC (Sheikh et al. 2020, Al-Jashamy et al. 2010, Abdulamir, Hafidh, and Bakar 2011). Several *in vitro* studies indicated that *S. bovis/gallolyticus* proteins trigger inflammatory cytokines production, which in turn result in the production of pro-carcinogenic ROS and RNS, and promoting angiogenesis (Abu-Ghazaleh, Chua, and Gopalan 2021). 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 (Dumke et al. 2017). Trimethylamine N-Oxide (TMAO) is a microbiota-derived metabolite associated with several disorders/diseases including IBD, PSC, metabolic syndrome, non-alcoholic fatty liver disease, and CRC (Barrea et al. 2018, Kummen et al. 2017, Wilson et al. 2015, Xu, Wang, and Li 2015, Sánchez-Alcoholado et al. 2020). TMAO is

produced by intestinal anaerobes 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 to be comparable in lacto-ovo-vegetarians and vegans (Janeiro et al. 2018, Obeid et al. 2017, Tomova et al. 2019). It has been shown that adherence to the Mediterranean diet, particularly rich in fruits and vegetables, may result in decreased TMAO levels (Obeid et al. 2017, De Filippis et al. 2016).

Gut microbiota are vital to maintain sufficient vitamin levels in the human body, which in turn are crucial to support gut homeostasis and prevent carcinogenesis. In particular, folate, riboflavin, and cobalamin (ie vitamins B9, B2, and B12), that are 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 (Song, Garrett, and Chan 2015, Tomova et al. 2019, Derrien and Veiga 2017). A metabolomic analysis by De Filippis et al. (De Filippis et al. 2016) showed an enrichment of folate biosynthesis in people following a Mediterranean or vegan diet compared with omnivores. Vegetable-rich dietary patterns have been also associated with an increased microbiota biodiversity and abundance (Laitinen and Mokkala 2019). This may be of particular importance considering that mucosa-associated gut bacteria in inflammatory bowel disease (IBD)-related colorectal cancer (CRC) subjects seem to be featured by an overall reduction in biodiversity (Richard et al. 2018). Recent studies have shown that high consumption of refined sugars may shift the balance of microbiota resulting in enhanced pro-inflammatory properties, reduced colonic epithelial integrity and mucosal immunity, which in turn can promote systemic low-grade inflammation and metabolic endotoxemia (Satokari 2020). According to this findings, high sugar intake has been associated with exacerbation of inflammation in IBD and CRC (Eppinga and Peppelenbosch 2016, Limdi, Aggarwal, and McLaughlin 2016, Hur et al. 2021). All these findings support a potential role of gut microbiota in the mediation of the link between diet, IBD

and CRC, suggesting that nutritional interventions might be employed in precision medicine and cancer prevention in IBD patients.

3.6 Nutritional factors influencing gut barrier function

A reduction in gut barrier function is currently 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, lipopolysaccharide, and other toxins through the barrier, resulting in intestine damage, enhancing inflammatory processes and release of ROS (Genua et al. 2021, McGuckin et al. 2009, Montalban-Arques and Scharl 2019, Shin and Kim 2018). Moreover, these bacteria or toxins may enter portal circulation promoting primary sclerosing cholangitis (PSC)(Dhillon et al. 2019) and non-alcoholic-fatty-liver-disease (NAFLD)(Cui et al. 2019), that are recognized risk factors for CRC in IBD-patients. Diet is an important modulator of gut barrier function, both directly by affecting intestinal epithelial cells junctions and consequently modulating permeability or indirectly by influencing the microbiota (Genua et al. 2021, Camilleri et al. 2019, Khoshbin and Camilleri 2020). The effects of diet components on the intestinal barrier function have been recently reviewed, focusing predominantly on human *in vivo* studies. They 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, non-digestible oligosaccharides, and proteins, help to preserve gut barrier function (Russo et al. 2012) 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 gut barrier and increase intestinal permeability, directly and indirectly promoting immune activation and inflammation in IBD (White, Ramos, and Kane 2021, Leclercq et al. 2014). Omega-3 and omega-6 PUFAs up-regulate expression of occludin, a TJ-protein, strengthen the epithelial barrier and

reducing gut permeability (Jiang et al. 1998, Durkin, Childs, and Calder 2021). It has also been shown that PUFAs can reverse TJ disruption caused by proinflammatory cytokines in Caco 2 intestinal cells (Beguin et al. 2013, Li et al. 2008, Amasheh et al. 2009). Thus, dietary patterns rich in Omega-3 and Omega-6 PUFAs, may have a role in the prevention of epithelial barrier alterations caused by inflammation or proinflammatory cytokines, and consequently in the prevention of CRC in IBD patients. Several studies employing human intestinal epithelial cell lines showed that dietary emulsifiers promote bacterial translocation and inflammation via epithelial TJ disruption (Fahoum et al. 2017, Roberts et al. 2010, Borthakur et al. 2007, Bhattacharyya et al. 2008, Borthakur et al. 2012, Choi et al. 2012). In addition accumulating evidences continue to show that dietary emulsifiers such as carrageenan, may be implicated in IBD inflammatory processes and thus in colitis-associated colorectal cancer (CAC) development (Bhattacharyya et al. 2017, Bancil et al. 2021, Naimi et al. 2021). Also endogenous surfactants such as bile acids, typically recognized for their roles in enabling the digestion and absorption of dietary lipids, may disrupt TJ proteins and thus increases gut permeability (Khoshbin and Camilleri 2020). Dysregulation of claudins (TJ proteins) relates with augmented intestinal permeability, perpetuation of inflammation, epithelial to mesenchymal transition, and tumour progression in IBD as well as subsequent CAC (Zhu et al. 2019). It is also suggested that claudins may act as signaling proteins and participate in cell differentiation, proliferation, and carcinogenesis through cellular signaling pathways (Günzel and Yu 2013). Some studies suggested a beneficial role for whey proteins in diseases characterized by intestinal barrier dysfunction (including IBD), in part, by modulating claudin expression (Kotler, Kerstetter, and Insogna 2013). It has also been shown that quercetin, a common flavonoid found in fruits, vegetables and grains, rises epithelial resistance in Caco-2 cell monolayers via upregulation of claudin 4 expression (Amasheh et al. 2008). Some human studies are starting to confirm the beneficial effect of dietary polyphenols (including flavonoids) on intestinal barrier function and microbiota homeostasis (Guglielmetti et al. 2020, Bernardi et al. 2020). In this regard, Del Bo et al.

have recently shown, for the first time, that a polyphenol-rich diet can reduce serum zonulin levels, an indirect marker of intestinal permeability (Del Bo et al. 2021).

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 (Liu et al. 2022). 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 tight junction molecules (Reunanen et al. 2015, Ashrafian et al. 2019), 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 (Gu et al. 2021). This organism seems to be sensitive to specific dietary factors (Dao et al. 2016) and human studies showed that Fermentable Oligo-, Di- and Mono-saccharides and Polyols (which includes fructose, lactose, oligosaccharides, and sugar alcohols) (FODMAP) content in diet might significantly increase *A. muciniphila* abundance possibly improving gut barrier function (Halmos et al. 2015, Halmos et al. 2016).

All these findings may represent a foundation for possible dietary treatments for the management of intestinal permeability, inflammation and gut function in IBD-patients, with the ultimate goal to prevent CAC.

3.7 Obesity, Metabolic Syndrome, hepatobiliary comorbidities and colorectal cancer

Although IBD has previously believed to be a condition characterized by undernourishment and low body mass index (BMI), cumulative evidences show that IBD does not strictly results in hyponutrition but frequently leads to malnutrition, with an increased risk of overweight or obesity in IBD patients, both adults and children (Long et al. 2011, Lomer et al. 2019). Visceral fat and related risk of metabolic syndrome has been linked with complicated and more severe disease course and increased rate of relapses in CD, thus suggesting that adipose tissue might exacerbate

inflammation in IBD (Pietrzyk et al. 2015). Obesity has been associated both with weak response to pharmacological therapies in CD and UC, and with CRC risk (Singh et al. 2017, Pietrzyk et al. 2015). Holtmann et al. (Holtmann et al. 2010) have also demonstrated better results after pharmacological treatment in UC patients with BMI kept under 25, indicating the benefit of body weight control in IBD patients through dietary interventions. In addition, obesity can lead to nonalcoholic fatty liver disease (NAFLD), a condition frequently found in IBD patients (Saroli Palumbo et al. 2019). Visceral obesity, dyslipidaemia, metabolic syndrome and NAFLD-related liver failure can promote CAC and CRC-liver metastasis (Gleeson and Anderson 2017, Lin et al. 2014, Pan et al. 2017, Lv, Patel, and Zhang 2019, Chen et al. 2021). Notably, high-fat diets increase secondary bile acids (BA) build-up, which are known risk factors for colonic inflammation and CRC, especially in Primary Sclerosing Cholangitis (PSC)-IBD patients, whose hepatic excretion of BA is impaired (Torres et al. 2011). BA can lead to ROS and RNS production, resulting in DNA damage, mutation and genomic instability in colonocytes (Bernstein et al. 2005). Although nutritional therapy has not been strictly explored in PSC, Suskind et al. (2018) (Suskind et al. 2018) suggest that diet may play a critical role for control and prevention of PSC in IBD patients, possibly influencing the risk for CAC. In particular they reported a case of clinical remission and normalization of laboratory parameters in a patient with UC and PSC using dietary therapy based on specific carbohydrate diet, which restricts complex carbohydrates from grains and eliminates refined sugar from the diet.

In addition to obesity, metabolic syndrome, and hepatobiliary conditions, malnutrition and especially micronutrient-deficiencies are considered to be risk factors for IBD severity and complications (Russell et al. 2021), including colitis-associated colorectal neoplasia. In particular, it has been shown that vitamin D deficiency is associated with poor outcomes in IBD patients and risk of CRC, (Gubatan and Moss 2018, Savoie et al. 2019) while low red blood cell folate is correlated with an enhanced risk of dysplasia and CRC in patients with UC (Lashner 1993). Moreover,

copper/zinc ratio imbalances have been associated with colon carcinogenesis (Stepien et al. 2017). Chicco et al. (2021) (Chicco et al. 2021) examined the impact of Mediterranean dietary pattern on the nutritional state, liver steatosis, clinical disease activity, and quality of life in IBD patients, including those with NAFLD. They observed a substantial lowering of malnutrition-associated parameters and liver steatosis in both CD and UC patients after a short-term nutritional intervention based on the adoption of MD, and this was accompanying with a spontaneous amelioration in inflammatory markers and disease activity. Cytokines secreted by adipose tissue or related with obesity, such as TNF-α and IL-6 play a pivotal role in a chronic state of systemic low-grade inflammation associated with CRC initiation and progression (Riondino et al. 2014). Low-fat diets have been demonstrated to decrease plasmatic levels of NFκB-regulated inflammatory cytokines and VEGF (Heymach et al. 2011, Calder et al. 2017).

4. Discussion

The incidence and prevalence of inflammatory bowel disease (IBD) is increasing worldwide. Despite the many therapeutic options, currently available pharmacologic therapies for IBD treatment have demonstrated only partial effects on CRC chemoprevention, and their systemic long-term toxicity has restricted their clinical application for this purpose (Chen, Shi, and Afzali 2019, Al-Bawardy, Shivashankar, and Proctor 2021). In addition, an early diagnosis of precancerous neoplasia in IBD is often difficult due to the contextual inflammation and the unavailability of sensitive biomarkers (Watanabe et al. 2011). For these reasons, dietary-based approaches are of vital importance not only to control IBD-associated symptoms but also as 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 IBD-patients, we have reviewed the possible role of nutrition and dietary bioactive compounds on IBD-

CRC and in particular on: 1. Genomic instability/stability, 2. IBD, inflammation and oxidative stress, 3. Primary Schlerosing cholangitis (PSC), 4. Microbiota and IBD, microbiota and IBD-related CRC, 5. Intestinal barrier function in IBD and CRC, and 6. Obesity, metabolic syndrome, NAFLD and IBD-related CRC.

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

Omega-3-PUFA, vitamin D, and SCFAs produced by anaerobic fermentation of dietary fibers, demonstrate favourable influences on the modulation of inflammatory processes, microbiota composition, gut-barrier, immune and metabolic function, potentially influencing IBD and colitis-associated carcinogenesis. Conversely, animal-derived fats, trans-unsaturated-fatty-acids (TFAs), micronutrients and vitamin deficiency/imbalance (for e.g. copper and zinc) can induce a pro-inflammatory effect, disrupting intestinal microbiota and barrier function, possibly promoting IBD and cancer.

The most important nutritional factors influencing the complex network underlying IBD-related CRC pathogenesis are schematized in Figure 2.

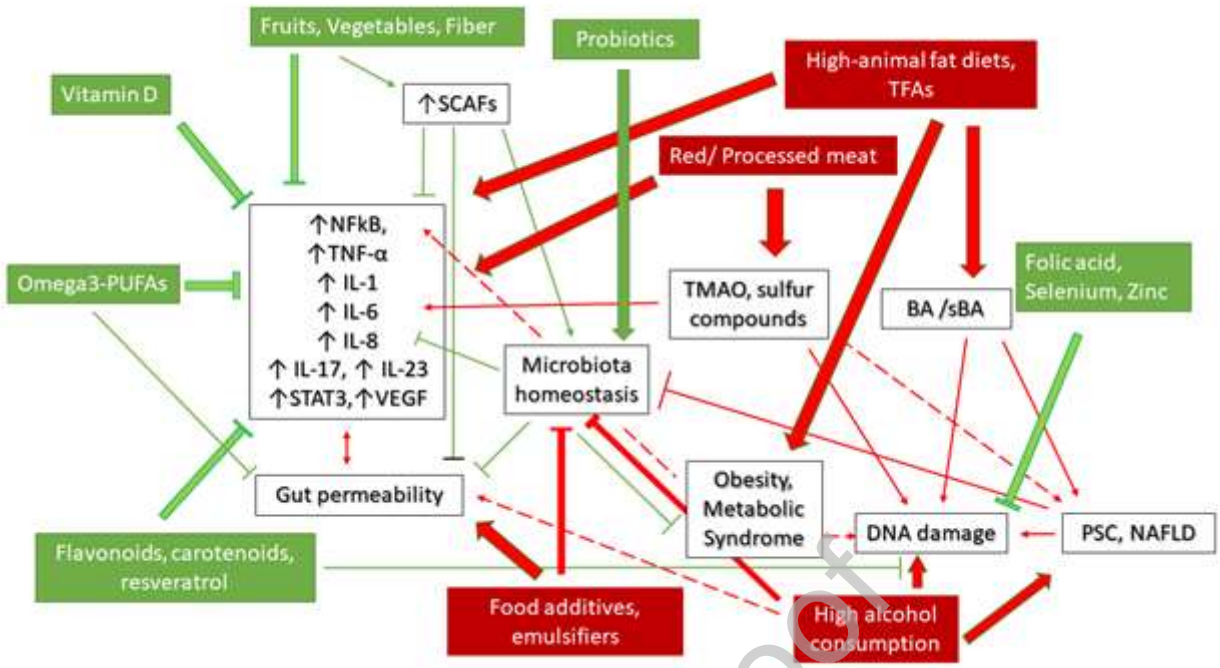

Figure 2. Schematic representation of the most important nutritional factors influencing the complex network underlying IBD-related CRC pathogenesis. Imbalanced, Western-like, high-animal fat diets elicit deregulation of inflammatory cytokines, promotes obesity and metabolic syndrome. Red and processed meat increases TMAO and sulfur compounds that lead to DNA damage and inflammation. Western dietary patterns are also 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 both directly by modulating inflammatory cytokines or indirectly by increasing SCFAs production and promoting microbiota homeostasis and reinforcing gut barrier. Vitamin D, Omega3-PUFAs, and plant-derived bioactive compounds such as flavonoids, carotenoids and resveratrol downregulate pro-inflammatory cytokines and/or enhance intestinal barrier function. Flavonoids, carotenoids and resveratrol also act as antioxidants protecting cells from DNA damage, resulting in an anti-cancer activity. Micronutrients such as folic acid, selenium and zinc have been shown to have a role in DNA repair processes. Probiotic supplementation helps in maintaining microbiota homeostasis and preserve intestinal barrier function. Abbreviations: BA, Bile Acids; IL, Interleukin; NAFLD, Non Alcoholic Fatty Liver Disease; PSC, Primary Sclerosing Cholangitis; sBA, Secondary Bile Acids; SCAFs, Short-Chain Fatty Acids; TFAs, Trans-Fatty Acids; TMAO, trimethylamine N-oxide; TNF-α, Tumor Necrosis Factor Alpha; VEGF, Vascular Endothelial Growth Factor.

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 (eg, omega-3-PUFAs, olive oil), low amount of animal proteins, raw and whole foods

(rather than refined ones) using fresh ingredients rather than pre-packaged foods, and probiotic supplementation, may be very useful to prevent gut inflammation and colitis-associated colorectal cancer (CAC). This cleaner dietary patterns also allow to avoid an overabundance of calories, minimizes intake of emulsifiers, refined sugars, and other artificial components characteristic of the Western diet that is linked to several disease conditions, including IBD and CAC. Unfortunately, IBD patients tends to consume substantially more animal protein, refined cereals, simple carbohydrates/sugars, dietary fat and cholesterol, and avoiding fibers in the 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 (Gerling et al. 2010, Rosman-Urbach et al. 2006, Zallot et al. 2013). Moreover, many clinicians tend to recommend low-intake/avoidance of fiber from fruits and vegetables in IBD patients, while there is no substantial evidence to support the benefit of this intervention (Brown, Rampertab, and Mullin 2011, Owczarek et al. 2016).

Although general dietary recommendations along with generic health behaviour prompt can help in preventing CRC in IBD-patients, there is no such thing as a perfect diet for everyone. For e.g., fibers are generally beneficial, but some patients with IBD report intolerance to some types of fiber (unfermented β-fructan) consumption. It has been hypothesized that fibers remain intact in selected patients with decreased fiber-fermenting gut microbes and can therefore bind host cell receptors, subsequently enhancing intestinal inflammation (Armstrong et al. 2022).

Personalised 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 colitis-associated cancer (CAC) (Hurtado-Lorenzo, Honig, and Heller 2020).

However, further research is needed to improve our 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-omics approaches including proteomics, metabolomics and metagenomics, represent expanding and promising tools to study the influence of dietary factors on health in a human biology-based and more physiologically relevant setting (Shinn and Holscher 2021, Aldubayan et al. 2022). This lays the foundations for a future personalized nutritional approach to the prevention of CRC in IBD-patients, taking into account the individual characteristics including genetic risk factors, specific inflammatory biomarkers, hepatobiliary and metabolic comorbidities, and microbiota composition.

5. Conclusions

Nutritional interventions based on healthy, nutrient-dense dietary patterns characterized by a high intake of fiber, vegetables, fruit, Omega-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 of 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 asset. In our view, it would be very important to stress more on how adequate dietary patterns are fundamental in assisting drug therapy and in reducing IBD-associated symptoms as a potential strategy to reduce the risk of IBD-related CRC. Targeted nutritional interventions which take into consideration individual risk factors, hepatobiliary and metabolic comorbidities, genetic characteristics and microbiota composition may represent a novel promising approach for the prevention and management of IBD-associated CRC.

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Declaration of interest

We have no conflict of interest to declare.

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