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REVIEW

Genetics, diet, microbiota, and metabolome: partners in crime for colon carcinogenesis

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Abstract

Colorectal cancer (CRC) ranks among the most prevalent malignant tumors worldwide, with a multifactorial etiology encompassing genetic, environmental, and life-style factors, as well as the intestinal microbiota and its metabolome. These risk factors often work together in specific groups of patients, influencing how CRC develops and progresses. Importantly, alterations in the gut microbiota act as a critical nexus in this interplay, significantly affecting susceptibility to CRC. This review highlights recent insights into unmodifiable and modifiable risk factors for CRC and how they might interact with the gut microbiota and its metabolome. Understanding the mechanisms of these interactions will help us develop targeted, precision-medicine strategies that can adjust the composition of the gut microbiota to meet individual health needs, preventing or treating CRC more effectively.

Keywords Colorectal cancer · Risk factors · Inherited predisposition · Diet · Obesity · Gut microbiota · Gut metabolome

Introduction

Colorectal cancer (CRC) is one of the most frequently diagnosed malignant tumors worldwide [1]. Its development, is influenced by unmodifiable risk factors, such as age, sex, inflammatory bowel disease (IBD), and genetic predisposition [2, 3], and modifiable risk factors, such as being overweight or obese, smoking, lack of physical activity, and unhealthy dietary habits [3, 4]. Together, these factors contribute to the complex multifactorial etiology to CRC. Increasing evidence indicates that changes in the gut microbiota, the community of microorganisms inhabiting the gastrointestinal (GI) tract, are implicated in the initiation and promotion of CRC [4] (Fig. 1).

Epidemiology

According to updated GLOBOCAN data (https://gco.iarc.who.int/en), CRC is the third most common cancer in terms of incidence and the second in mortality globally, with over 1.9 million new cases and 904,000 deaths in 2022. These figures are expected to rise to 3.2 million cases and 1.6 million deaths by 2040 [5]. The age-standardized incidence rate worldwide is 21.9 per 100,000 cases in males and 15.2 in females (https://gco.iarc.who.int/en).

Global CRC incidence and mortality rates are increasing, reflecting the aging population and changes in the prevalence and distribution of CRC risk factors associated with socioeconomic development [1]. Developed countries, such as Europe, Oceania, Northern America, and Eastern Asia, have a higher CRC risk compared to less developed areas, such as Africa, Southern Asia, and Latin America. However, recent advances in early detection and treatment options, as well as lifestyle modification, are aiding in the reduction of CRC mortality in developed countries [6]. Nevertheless, also within the same country there could be some epidemiological differences. Paradigmatic examples are the higher CRC incidence and mortality rates of Black Americans and Alaska Natives *vs* other U.S. ethnic groups, which can be likely explained by lifestyle factors linked to socioeconomic

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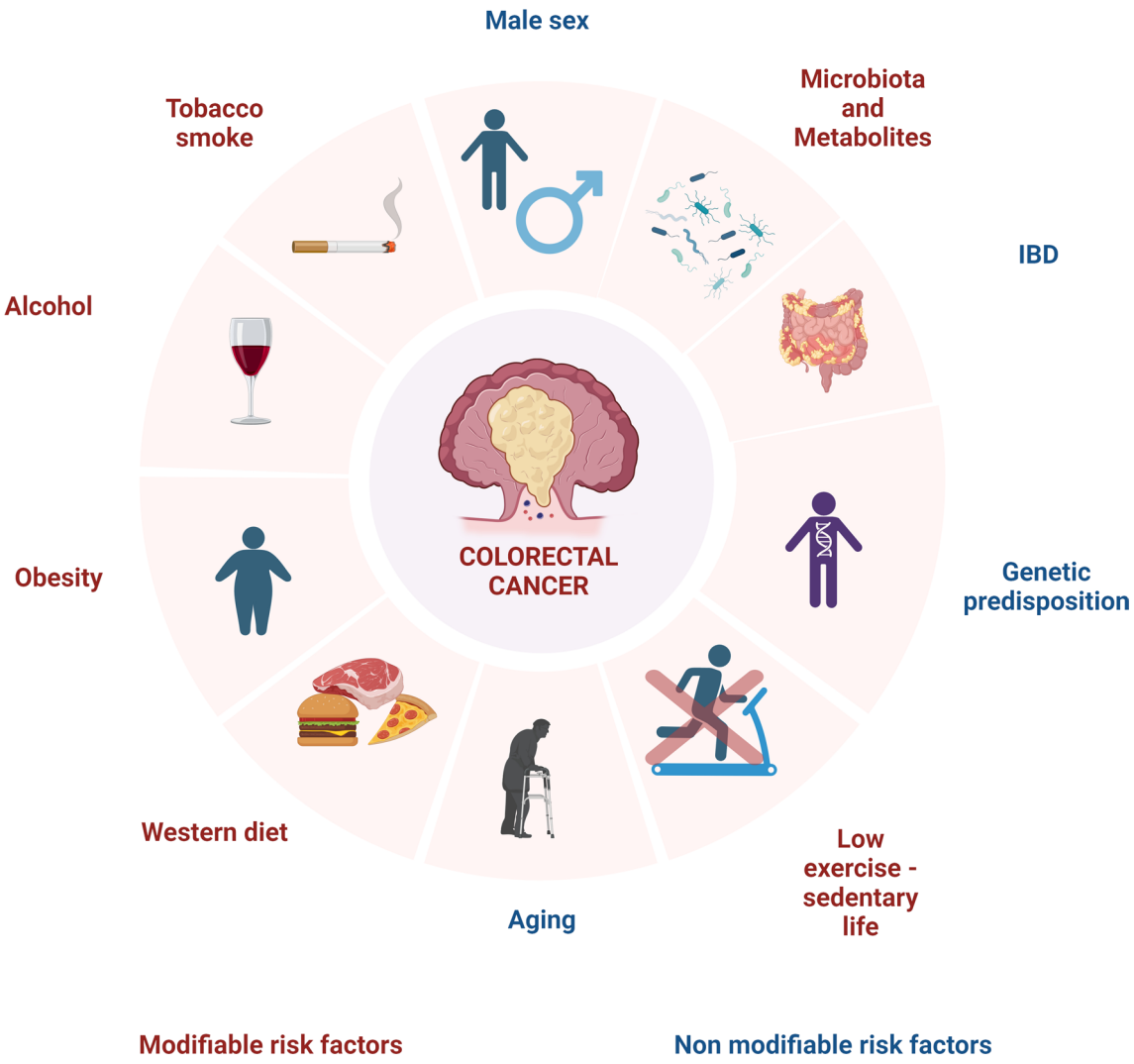

Fig. 1 Risk factors for CRC. The unmodifiable risk factors are indicated in blue, while the modifiable risk factors are highlighted in red (created with BioRender.com). Abbreviations: IBD, inflammatory bowel disease

inequalities and diet, disparities in the access to screening programs, and genetic factors [7, 8].

Pathobiology

Carcinogenesis typically unfolds in four steps: (i) initiation, where genetic alterations makes cells more susceptible to neoplastic transformation; (ii) promotion, involving the abnormal growth of the initiated cells; (iii) progression, characterized by further genetic and epigenetic alterations that increase the rate of cell growth; and (iv) metastasis, the spread of cancer cells to other organs, generally the liver and lungs [9].

Most colorectal cancers (85–90%) arise from a multistep process, known as the "adenoma-carcinoma sequence", which begins with changes in epithelial cells that first transform into adenomas and later progress into adenocarcinomas. We also know that about 10–15% of CRCs emerge from the so-called serrated pathway, originating from serrated polyps, while < 2% of CRCs arise from chronic inflammation, known as the inflammatory pathway [9].

There are two main precursors to CRCs, adenomatous polyps (*i.e.*, adenomas) and serrated polyps [10]. Adenomatous polyps, which can be tubular, villous, or tubulovillous [11], pose a high risk of becoming adenocarcinomas as they grow, especially those ≥ 1 cm [12]. Serrated polyps are heterogeneous lesions that include hyperplastic polyps (HP), traditional serrated adenomas (TSA), sessile serrated adenomas (SSA), and mixed polyps, with only a subset of HPs progressing into serrated adenomas and CRCs [9, 13].

CRCs are also categorized based on their anatomical location: (i) proximal to the splenic flexure or right-sided, which includes tumors in the cecum, ascending colon,

hepatic flexure, or transverse colon, (ii) distal or left-sided, occurring in the descending or sigmoid colon; and (iii) rectal, emerging within 15 cm from the rectum [14, 15]. The risk of developing proximal or distal tumors varies with factors such as age, sex, genetics, and ethnicity [16]. Proximal CRCs are more frequent in females, older individuals, and those of African and Afro-American descent, while distal colorectal cancers are more common in males, younger individuals, and those of Caucasian ethnicity [9].

Genomic instability

Genomic instability, defined by the gradual accumulation of genetic and epigenetic aberrations, plays a central role in CRC development through three different mechanisms: chromosomal instability (CIN), microsatellite instability (MSI), and CpG island methylator phenotype (CIMP) [9].

Chromosomal instability

Accounting for almost 80–85% of CRC cases [17], the CIN pathway is characterized by the presence of structural and numerical chromosomal abnormalities and loss of heterozygosity (LOH). It often involves mutations in the tumor-suppressor gene *APC*, with ensuing hyperactivation of the Wnt/β-catenin signaling pathway, leading to tumor development. Normally, the APC protein forms part of a multiprotein destruction complex, which also includes axis inhibitor (axin), protein phosphatase 2A, glycogen synthase kinase-3 beta (GSK3β), and casein kinase 1 (CK1), which in the absence of WNT ligand, promotes proteasomal degradation of the transcription factor β-catenin, preventing cell proliferation and initiating differentiation [18]. However, loss of function (LOF) mutations in *APC* or other components of this complex or the presence of the WNT ligand can prevent this degradation, allowing β-catenin to accumulate, translocate into the nucleus, and trigger uncontrolled cell proliferation [17]. The same effect may be due to an activating mutation in β-catenin [19]. Such cells may further mutate, acquiring changes in other genes, including the oncogene *KRAS*, whose mutations constitutively activate MAP kinase signaling to increase cell proliferation, as well as the tumor-suppressor *TP53*, leading to higher-grade adenomas and eventually adenocarcinomas [17].

Microsatellite instability

MSI, found in about 15% of CRC cases, is characterized by variations in the number of repeats of microsatellites, which are short tandem DNA sequence repeats in the tumor tissue. This instability typically stems from the somatic inactivation of both alleles of one mismatch repair (MMR) gene (e.g., *MLH1, MSH2, MSH6* or *PMS2*) in sporadic CRCs. Alternatively, in patients with Lynch syndrome, MSI can result from a germline mutation in one of these MMR genes followed by somatic inactivation of the remaining functional allele [20].

There are two distinct MSI tumor phenotypes: MSI-high (MSH-H) and MSI-low (MSI-L), which are defined by the degree of instability in microsatellite markers [20]. Intriguingly, the presence of MSI is associated with a better outcome in sporadic CRC compared to microsatellite stable (MSS) tumors [21].

CpG island methylator phenotype

CpG island methylator phenotype (CIMP) is caused by hypermethylation of CpG islands at the promoters of tumor-suppressor genes, leading to gene silencing, which in turn promotes cell proliferation and inhibits apoptosis [22, 23]. Hypermethylation of CpG islands is commonly linked to the serrated pathway of colorectal carcinogenesis [9].

Risk factors

Sex and age

The risk of CRC increases with age and is higher in males than in females. However, females are more susceptible to the highly aggressive right-sided colon cancers [6]. To explain sex-related disparities in CRC incidence, besides dietary and lifestyle habits, a role for sex hormones has been proposed. In particular, a protective role for estrogens has been linked with their involvement in control of cell proliferation and epithelial–mesenchymal transition pathways [24, 25]. Also gender differences, due to the chosen sexual identity that influences behavior and lifestyle, may have an impact on CRC risk [24, 25]. For example, women generally consume more vegetables and fiber and less alcohol than men [26, 27].

The incidence of CRC development and mortality increases after the age of 50.

While CRC incidence in older individuals has decreased over the past few decades, it has increased among those under 50 years, likely due to more sedentary lifestyles and greater adherence to the Western diet [6]. A significant number of CRC cases in younger individuals (under 50 years old) are attributed to genetic predisposition [28]. Early-onset CRCs (EOCRC), occurring before 50 years of age, are usually diagnosed in more advanced stages, mainly because of the lack of screening programs for young individuals, which prevents early CRC detection. Considering that EOCRC incidence is increasing since the last decade of the twentieth century, a younger age to access screening should be considered and it is mandatory to spread and support lifestyle

habits that prevent CRC since childhood (*e.g.* limiting fried and processed food consumption, avoiding alcohol abuse and smoking) [29].

Genetic predisposition

A positive familial history poses a significant CRC risk factor, observed in about 30% of cases [30, 31]. The risk increases with the number of affected family members, their age at diagnosis, and their closeness of kinship [32]. Nonetheless, only 2–8% of CRC cases, both polyposic and non-polyposic, are associated with germline pathogenic variants in high-risk cancer genes, known as monogenic syndromes [31, 33]. The main hereditary monogenic CRC syndromes are detailed in Table 1 and described below.

Lynch syndrome and constitutional MMR deficiency syndrome

Lynch syndrome, originally known as hereditary nonpolyposis colorectal cancer (HNPCC), is an autosomal dominant inherited syndrome that accounts for 3% of CRC cases. Typically, CRC onset in LS patients occurs at around 45 years of age, predominantly in the proximal (right-sided) colon, progressing rapidly. LS also increases the risk of extra-colonic malignancies, such as endometrial and ovarian cancers [34]. It results from germline monoallelic loss-of-function mutations in MMR genes—*i.e.*, *MLH1* (42% of variants), *MSH2* (33%), *MSH6* (18%), and *PMS2* (7.5%) [31]—or by deletion of the *EPCAM* gene, leading to the silencing of its neighboring gene *MSH2* [35]. *MLH1* can also be silenced by constitutional epimutation, achieved through *MLH1* promoter methylation [36].

MLH1 pathogenic variants (PVs) are associated with the highest risk of CRC, with *MSH2* variants also presenting a significant risk when compared to *MSH6* or *PMS2* variants. In addition, PVs in *MSH2* carry the greatest risk for extracolonic cancers, particularly endometrial cancer [37].

The presence of heterozygous germline mutations in MMR genes predisposes to a second somatic mutation in the wild-type allele, leading to deficient mismatch repair (dMMR) tumors characterized by MSI [38]. LS is associated with up to an 80% risk of developing microsatellite unstable cancer. dMMR tumors can also be of sporadic origin [39]. The loss of expression of an MMR gene causes genetic instability and the acquisition of a plethora of somatic mutations, including loss of APC [40].

Biallelic germline PVs in an MMR gene, including *MSH3* and *MLH3*, cause constitutional MMR deficiency syndrome (CMMRD), a rare hereditary monogenic cancer syndrome characterized by a high risk of early-life malignancies and often accompanied by polyposis conditions, with up to 100 synchronous adenomas or juvenile-like polyps [33].

Familial adenomatous polyposis

Familial adenomatous polyposis (FAP) is responsible for less than 1% of CRC cases and causes the development of hundreds to thousands of polyps throughout the colon—mostly on the left side—and rectum, starting from a young age (7–36 years). About 95% of individuals with FAP develop polyps by age 35 [41, 42].

The attenuated form of FAP, known as attenuated familial polyposis (aFAP), is characterized by a lower number of polyps (< 100) that occur around ages 50–55 [41]. Both FAP and aFAP arise from germline heterozygous PVs in different domains of *APC*, a key regulator of cell growth, cellular

Table 1 Classification of monogenic CRC syndromes into polyposis and non-polyposis types. Syndromes with autosomal dominant inheritance are highlighted in bold

	Syndromes	Genes
Monogenic non-polyposis syndromes	**Lynch syndrome (LS)**	mismatch repair genes (*MLH1, MSH2, MSH6, PMS2*), *EPCAM*
	Familial colorectal cancer type X syndrome (FCCTX)	See Sect. "Familial colorectal cancer type X"
Monogenic polyposis syndromes	**Familial adenomatous polyposis (FAP)**	*APC*
	Polymerase proofreading-associated polyposis (PPAP)	*POLE, POLD1*
	MUTYH-associated polyposis (MAP)	*MUTYH*
	NTHL1-associated polyposis (NAP)	*NTHL1*
	Constitutional MMR deficiency syndrome (CMMRD)	*MLH1, MSH2, MSH6, PMS2, MSH3, MLH3*
	Hamartomatous polyposis syndromes:	
	Peutz–Jeghers syndrome (PJS)	*STK11*
	Juvenile polyposis syndrome (JPS)	*BMPR1A, SMAD4*
	PTEN hamartoma tumor syndrome (PHTS)	*PTEN*
	Serrated polyposis syndrome (SPS)	*RNF43*

adhesion, and cytoskeleton stabilization [42], as well as a major tumor suppressor in colorectal carcinogenesis.

Hamartomatous polyposis syndromes

Hamartomatous polyposis syndromes are rare autosomal dominant hereditary syndromes, leading to the formation of hamartomatous polyps in the GI tract. These include Peutz–Jeghers syndrome (PJS), juvenile polyposis syndrome (JPS), and PTEN hamartoma tumor syndrome (PHTS) [43]. The histology of hamartomatous polyps enables the differentiation between Peutz–Jeghers polyps, which are typically multilobulated and covered by hyperplastic glandular mucosa, and juvenile polyps, which are spherical and include inflammatory cells [44].

Most Peutz–Jeghers cases (94%) are due to germline mutations in the *STK11* tumor suppressor gene, which is involved in mTOR signaling. In contrast, juvenile polyposis syndrome is caused by germline heterozygous mutations in *BMPR1A* (~28%) and *SMAD4* (~27%), while 45% of cases have no established genetic cause [44, 45]. PHTS comprises various clinical entities characterized by the overgrowth of multiple hamartomas across several organs, typically due to a germline pathogenic *PTEN* variant [46].

MUTYH-associated polyposis

MUTYH-associated polyposis is an autosomal recessive hereditary syndrome stemming from homozygous or compound heterozygous germline PVs in the *MUTYH* gene [47], which encodes a DNA glycosylase involved in the base excision repair (BER) pathway. In particular, this enzyme excides the adenine incorrectly paired with 8-oxoG derived from oxidative damage [47]. The phenotypes associated with MAP are highly variable, ranging from 1–10 colon adenomas before 40 years of age, to 10–100 colon adenomas and/or hyperplastic polyps, to over 100 colon polyps without a germline *APC* mutation [48]. Carriers of heterozygous PVs in *MUTYH* with a family history of CRC are at an increased risk of developing CRC as well as other cancers, such as gastric and endometrial cancers [49].

NTHL1-associated polyposis

NTHL1-associated polyposis (NAP), similar to *MUTYH*, is due to biallelic germline mutations in *NTHL1,* another gene involved in the BER pathway. NAP is characterized by an increased risk of developing colorectal polyposis (1–100 polyps), CRC, and breast cancer [50, 51]. Although polyposis generally occurs in homozygous individuals, some heterozygous ones also develop cancer and show loss of heterozygosity in tumor tissues [33, 51].

Polymerase proofreading-associated polyposis

Polymerase proofreading-associated polyposis (PPAP) is marked by multiple colorectal adenomas and CRC and originates from heterozygous missense PVs in the exonuclease domains of *POLE* and *POLD1* genes. These mutations in the exonuclease domain impair the proofreading function of these polymerases during DNA replication, leading to a high rate of misincorporated bases [33, 52].

Serrated polyposis syndrome

The serrated polyposis syndrome (SPS) is characterized by multiple serrated colorectal polyps, which are precursors of about 15% of CRCs through the serrated pathway. Although the genetic causes of SPS are not fully understood, heterozygous loss-of-function mutations in *RNF43*, a RING-type E3 ubiquitin ligase, have been reported [33, 53]. Since *RNF43* is an inhibitor of the Wnt pathway, this syndrome underscores once more the important role of the Wnt pathway in colon carcinogenesis.

Familial colorectal cancer type X

Familial colorectal cancer type X (FCCTX) is characterized as a form of colorectal cancer that occurs in families, exhibits normal MMR function, and does not typically present with multiple polyps. It involves a diverse monogenetic background [31]. Mutated genes include *BMPR1A, RPS20, SEMA4A, SETD6, BRCA2, OGG1*, *FAN1, CENPE, CHD18, GREM1, BCR, KIF24, GALNT12, ZNF367, HABP4, GABBR2, BMP4, APC, NTS, TP53,* and *SMAD4* [54, 55]. Noteworthy, some of those genes (*e.g.*, *APC, BMPR1A,* and *SMAD4*) are also linked to polyposis syndromes.

Most genes are involved in DNA repair. *OGG1*, for instance, encodes 8-oxoguanine glycosylase, an enzyme essential for the base excision repair pathway that fixes oxygen-reactive DNA lesions [55]. BRCA2, part of the Fanconi anemia pathway, and the nuclease FAN1 are involved in interstrand DNA cross-link repair [56, 57].

RPS20 encodes a protein component of the small ribosome subunit. A frameshift variant in this gene was found in a four-generation FCCTX Finnish family co-segregating with CRC, and all studied tumors were MMR proficient [58]. In addition, two other cases appeared in a cohort of 863 early onset/familial CRC patients [59]. Heterozygous loss-of-function variants in ribosomal protein (RP) genes cause Diamond Blackfan anemia (DBA), a syndrome characterized by cellular hypo-proliferation due to ribosomal dysfunction [60]. DBA is linked to a higher incidence of CRC, the most prevalent solid tumor in young adults with DBA [61, 62]. The connection between DBA and CRC may involve a selective advantage

for clones with inactivating somatic *TP53* mutations in a generally hypoproliferative environment due to p53 stabilization [62].

GALNT12 encodes the enzyme N- acetylgalactosaminyltransferase-type 12 involved in the O-glycosylation of mucin-type glycans, essential components of the intestinal mucous barrier. Loss-of-function variants in *GALNT12* confer a moderate susceptibility for CRC with an autosomal dominant pattern of inheritance [31, 63–65], as well as *SEMA4A,* which encodes for a semaphorin receptor with immunomodulatory effects and growth regulatory functions [66].

Inflammatory bowel disease

Inflammatory bowel disease (IBD), which encompasses chronic inflammatory conditions of the GI tract, including ulcerative colitis (UC) and Crohn's disease (CD) [67, 68] significantly increases the risk of CRC. This risk escalates with the duration of the disease, with studies showing a cumulative incidence of 18% at 30 years for UC patients [69]. IBD is also characterized by chronic, relapsing inflammation of the GI tract, which leads to persistent epithelial damage and regeneration, increasing the likelihood of DNA mutations.

Pro-inflammatory cytokines, reactive oxygen species (ROS), and other inflammatory mediators contribute to genetic instability, leading to colitis-associated colorectal cancer (CAC) [70]. The inflammatory environment in CAC favors genetic mutations in key oncogenes and tumor suppressor genes. Common alterations include mutations in the *TP53* gene, which occur earlier in CAC than sporadic CRC, along with alterations in the *KRAS* and *APC* genes [71]. Moreover, epigenetic modifications, such as DNA methylation and histone changes, also play a role in CAC development [71].

IBD is typified by a dysregulated immune response that creates a pro-tumorigenic microenvironment, where cytokines such as TNF-α, IL-6, and IL-23 promote tumor growth and survival by activating tumorigenic pathways regulated by NF-κB and STAT3 transactivation of downstream effectors [72]. Furthermore, dysbiosis and reduced gut microbiome diversity are common features in IBD (see Sect. "Gut microbiota and metabolome"). This condition is characterized by an increased presence of Bacteroidetes and Proteobacteria, including Enterobacteriaceae and Bilophila, accompanied by a reduction in *Faecalibacterium prausnitzii* and other Firmicutes [73, 74]. Dysbiosis in these patients likely leads to an impairment of the intestinal barrier integrity and gut homeostasis, further driving inflammation and carcinogenesis.

Sedentary lifestyle

Physical inactivity and a sedentary lifestyle are well-known CRC risk factors [75]. The prevalence of a sedentary lifestyle has increased due to more office-based work and lifestyle changes, such as extended periods of sitting and increased screen time [76]. The shift toward smart-working after the COVID19 pandemic has further exacerbated this trend [77]. As sedentary lifestyle can contribute to colorectal carcinogenesis by adiposity accumulation and metabolic dysfunction [78], the American Cancer Society (ACS) recommends engaging in moderate-intensity activity for at least 150 min or vigorous-intensity for 75 min throughout the week [9], which can reduce the risk of CRC by over 20% [79]. The beneficial effect may be ascribable to positive effects on gut motility, metabolic hormone regulation, tissue oxygenation, basal metabolism and the immune system [9]. In particular, natural killer (NK) cells and CD8 + T cells are mobilized to the circulation during physical exercise, improving the antitumoral immune function [80–82]. The suppression of inflammation and of proliferative signaling pathways also contribute to exercise-related CRC prevention [79]. Activities that improve blood flow and skeletal muscle function, such as standing and moderate exercise, enhance glucose regulation and contribute to reduce fat accumulation [76]. Regular exercise mediates the release into the circulation of myokines, *i.e.* molecules produced by skeletal muscles during physical activity. For example, exercise-mediated release of IL-6 is reported to inhibit tumor cell proliferation and irisin has been correlated to apoptosis of cancer cells [82]. Another myokine, named SPARC, is involved in the inhibition of colon tumorigenesis by activating apoptotic proteins [83]. These combined effects contribute significantly to overall health and disease prevention.

Cigarette smoking

According to the World Cancer Research Fund (WCRF) and American Institute of Cancer Research (AICR), smoking 40 cigarettes per day increases CRC risk by up to 40% and doubles CRC mortality rate compared to non-smokers. Former smokers retain a higher risk to develop CRC compared to non-smokers, even if they have stopped smoking for more than 25 years [84].

Cigarette smoke, which contains a mixture of toxic compounds, such as polynuclear aromatic hydrocarbons, nitrosamines, and aromatic amines, reaches the colorectal mucosa through the circulatory system or direct ingestion, inducing genetic and epigenetic aberrations that heighten the risk of CRC [85].

Obesity

Obesity, defined by the World Health Organization (WHO) as "abnormal or excessive fat accumulation that may impair health," is closely linked to chronic inflammation and excessive adipose tissue expansion [86].

Adiposity is typically assessed using body mass index (BMI), calculated as body weight in kilograms divided by the square of height in meters, and waist circumference (WC) [87]. A BMI of ≥ 25 kg/m^2 classifies an individual as overweight, while a BMI of ≥ 30 kg/m^2 indicates obesity. It has been reported that each 5 kg/m^2 increase in BMI is associated with 5% increased risk for CRC [4]. Notably, visceral adipose tissue (VAT), compared to subcutaneous adipose tissue (SAT), is more closely associated with CRC [9, 87]. Importantly, WC, an indicator of visceral fat, is a stronger CRC risk factor than BMI alone [88, 89].

Adipose tissue functions as an active endocrine and metabolic organ that affects the physiology of other tissues through the secretion of free fatty acids, adipokines, and cytokines [90]. The primary endocrine adipokines produced by adipose tissue are leptin, which is a proinflammatory hormone that suppresses appetite, increases basal metabolism, and has levels proportional to the adipose tissue volume, and the insulin sensitizing hormone adiponectin, which exerts anti-inflammatory activity and is inversely correlated with BMI [86, 90]. Leptin stimulates cell proliferation, migration, and invasion through the PI3K/AKT/mTOR pathway, supporting tumor development [86]. Conversely, adiponectin inhibits cell proliferation by activating the AMPK signaling pathway, and its reduction is linked to CRC development [86]. Furthermore, VAT is densely populated with immune cells, such as lymphocytes and M1 macrophages, which induce chronic low-grade systemic inflammation and insulin resistance [9], conditions associated with oxidative stress and cancer initiation and progression [86].

In the lean state, healthy adipose tissue is enriched with anti-inflammatory immune cells that help reduce inflammation. However, as obesity develops, the secretion of inflammatory cytokines, including interleukin 1β (IL-1β), interleukin 6 (IL-6), and tumor necrosis factor α (TNF-α) increases, leading to enhanced inflammation within the adipose tissue [86].

Obesity-related inflammation causes insulin resistance, characterized by a reduced tissue response to insulin and subsequent hyperinsulinemia, a compensatory mechanism to maintain normal blood glucose levels [90]. In obese individuals, hyperinsulinemia triggers downstream signaling of insulin-like growth factor (IGF) receptors, which in turn activates PI3K, mTOR, and MAPK pathways, promoting cell proliferation and inhibiting apoptosis of colon epithelial cells [91].

Obese individuals often display intestinal dysbiosis. Efforts to modify the intestinal microbiota in obese or diabetic individuals include the administration of *Akkermansia muciniphila*, which has shown a beneficial effect on insulin resistance [92].

Unhealthy diet

An unhealthy dietary pattern, often exemplified by the Western diet, is rich in red and processed meats, added sugars, sugarsweetened beverages, desserts, refined grains, and potatoes [9]. Such unhealthy dietary habits are associated with an increased risk of CRC, as well as higher rates of tumor recurrence and mortality [93–95]. Conversely, a healthy or prudent diet, characterized by a high intake of fruits, vegetables, whole grains, low-fat dairy products, and fish, supports overall health and reduces CRC risk [9]. The Western diet has been associated with intestinal dysbiosis, whereas the Mediterranean diet, known for its low saturated fat and high fiber content, promotes eubiosis, thereby contributing to a healthier gut microbiota [96].

Red and processed meat

Consumption of red and processed meats is linked to an elevated risk of CRC [4, 97]. To accurately assess this risk, it is essential to consider various aspects of meat consumption, such as quantity, type (*i.e.*, fresh, red, or white), and methods of processing and cooking. Several mechanisms have been proposed to explain how red and processed meat consumption increases CRC risk:

1. Genotoxic compounds, such as heterocyclic aromatic amines (HAAs) and polycyclic aromatic hydrocarbons (PAHs), are considered genotoxic because they act directly on DNA, causing mutations [98]. These compounds form when the meat is being cooked at high temperatures [99];
2. N-nitroso compounds (NOCs), comprising nitrosamines, nitrosamides, and nitrosoguanidines can induce DNA →AT transitions and are formed exogenously during meat or food processing and endogenously by reactions catalyzed by the intestinal microbiota [100, 101]. Found in bacon, cured meats, sausages, ham, smoked fish, and smoked cheeses, these compounds are typically present under conditions such as humid storage, nitrogen-saturated air smoking, high-temperature drying, and curing with nitrate and/or nitrite [102]. Endogenously, NOCs are generated within the colon after consuming red meat rich in heme [103];
3. Heme iron, abundant in meat, promotes proliferation of colonocytes [98]. Through N-nitrosation, it contributes to the endogenous formation of NOCs [100, 101].

Dietary heme iron also augments lipid peroxidation and free radical formation [104], causing DNA strand breaks and oxidative DNA damage [105];

4. Trimethylamine-N-oxide (TMAO) is a gut metabolite implicated in triggering inflammation and stimulating cell proliferation [106]. It originates from animal-based foods [107]. The process begins with gut microbiota converting choline, phosphatidylcholine, and L-carnitine into trimethylamine (TMA). Once formed, TMA is transported to the liver, where it is oxidized to TMAO [108], which plays a role in promoting changes that can influence disease processes, including the development of CRC;
5. Dietary fat and bile acids. Increased meat intake, particularly red and processed meats, is associated with higher fat consumption, which can lead to insulin resistance and an increase in the production of secondary bile acids (BAs) [98]. Specifically, a high-fat diet, promotes the secretion of primary BAs that are then metabolized by the gut bacteria into secondary BAs [4], inducing oxidative DNA damage, metabolic stress, and membrane perturbation. The resulting cascade of reactions produces reactive oxygen and nitrogen species, creating a microenvironment conducive to CRC development [109].

Added sugar and sugar-sweetened beverages

Added sugar, such as high fructose corn syrup (HFCS) or sucrose, are commonly added to foods and beverages. Sugar-sweetened beverages (SSBs), which include soft drinks, fruit drinks, and sports drinks [110], are significant sources of these added sugars. Particularly in adolescence, high intake of SSBs and other added sugars may alter the insulin-like growth factor axis, leading to insulin resistance, obesity, type 2 diabetes, and increased inflammation, all of which can contribute to the development of CRC [111, 112].

Fructose, a predominant, ingredient in SSBs, unlike glucose, is mainly metabolized in the liver. High consumption of fructose, particularly from HFCS-sweetened beverages, triggers hepatic lipogenesis [110]. Studies using Apc-deficient mice have shown that even low doses of fructose, which do not cause obesity or metabolic dysfunction, can result in a higher incidence and grade of colon tumors compared to controls [113]. Fructose consumption enhances glycolysis and fatty acid synthesis in tumors, supporting their growth [113]. Finally, dietary fructose in mice on a high-fat diet has been shown to promote intestinal cell survival and villous hypertrophy, increasing nutrient absorption and adiposity [114], thereby exacerbating conditions favorable for cancer development.

Alcohol consumption

Alcohol consumption is linked to an increased CRC risk in a dose-dependent manner [6]. Consuming two or three alcoholic beverages per day (~30 g/day) raises the CRC risk by 20%, while heavier consumption can double the risk to 40% [6]. Ethanol, the primary component of alcoholic beverages, is a known CRC risk factor primarily due to its first metabolite, acetaldehyde, which the International Agency for Research (monographs.iarc.who.int) classifies as a Group 1 carcinogen.

Once ingested, alcohol reaches the colonocytes through systemic circulation and may diffuse into the lumen, where it is metabolized by alcohol dehydrogenase into acetaldehyde. This metabolite can cause mucosal damage and stimulates cell proliferation. In addition, acetaldehyde can penetrate intestinal epithelial cells, promoting colorectal carcinogenesis by inducing DNA damage and reducing absorption of folate (vitamin B9), required for proper DNA synthesis and methylation [9, 115].

Other mechanisms implicated in alcohol-induced carcinogenesis include:

1. Increased gut permeability. Excessive ethanol consumption impairs gut barrier functions [116], allowing the passage of other environmental carcinogens (*e.g.*, aflatoxins, benzene, asbestos, etc.) and bacteria [117];
2. Induction of inflammation. In mice, ethanol induces inflammation in the colonic mucosa and submucosa, increasing the production of pro-inflammatory cytokines (*i.e.*, IL-1α, IL-6, and TNF-α) [118]. The interaction between ethanol and the gut microbiota enhances this inflammatory response, as demonstrated by in vitro studies showing that high ethanol concentration increases pro-inflammatory cytokine production in synergy with *E. coli* [116];
3. DNA adduct formation. This process is mediated by cytochrome P450 2E1 (CYP2E1) [117], whose catalytic activity stimulates ethanol metabolism resulting in ROS, which are responsible for lipid peroxidation and DNA adduct formation [119];
4. Epigenetic alterations. Alcohol consumption can lead to epigenetic changes by reducing folate absorption and metabolism [120]. Lower levels of vitamin B9 can cause aberrant DNA methylation, further contributing to carcinogenesis [121].

Protective factors

Protective factors for CRC include physical activity, prudent diet (high consumption of fruit, vegetables, fish, and wholegrain products), and non-steroidal anti-inflammatory drugs (NSAIDs) [122].

Fruit and vegetables

The World Cancer Research Fund (WCRF) states that fruits and vegetables are associated with a reduced CRC risk, albeit the evidence is considered "limited." The Continuous Update Project (CUP) reviewed 17 studies on the relationship between fruit and vegetable intake and CRC risk. Ten of those studies were included in a dose–response meta-analysis, which demonstrated an inverse association for each 100 g/day of fruits.

Fruits and vegetables are rich in bioactive compounds like polyphenols, flavonoids, and soluble fiber, along with vitamins and minerals. A recent meta-analysis supports the hypothesis that high consumption of these foods offers protective effects against CRC, largely due to high levels of flavonoids [123]. These compounds likely confer benefits through their anti-inflammatory, antioxidant, and pro-apoptotic properties [124].

Anthocyanins, water-soluble pigments found in many fruits and vegetables, are thought to play a role in CRC prevention thanks to their ability to downregulate some inflammatory pathways, such as NF-κB, MAPK, and JNK, and inhibit the Wnt signaling pathway, exerting an anti-proliferative effect [125].

Fruits and vegetables also contain vitamins, especially vitamin Bs, which are crucial for DNA synthesis, repair, and methylation [126]. In mice models, vitamin B6 has been shown to reduce polyp formation in the colon and to suppress cell proliferation, mechanisms central to CRC prevention [127, 128].

High dietary intake of folate, particularly from deep green leafy vegetables, is associated with reduced risks of CRC and adenoma. However, the protective effects of folate supplementation remain controversial [129, 130]. Indeed, folate serves as a methyl donor in DNA methylation, a process often impaired in the early stages of CRC. In particular, excessive hypermethylation of CpG sites in gene promoters, a common occurrence in CRCs, leads to the silencing of these genes [131]. Lastly, niacin, or vitamin B3, is known for its hypolipidemic and anti-inflammatory effects. Studies in mice suggest that niacin supplementation can prevent colitis and CRC [132, 133].

Fish and omega-3

Consumption of fish is linked to a 12% reduction of CRC risk [134], mainly due to its high content of vitamin D and omega-3 fatty acids [98]. Polyunsaturated fatty acids are classified into omega-3 and omega-6 groups. Omega-3 fatty acids, including α-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) are endowed with anti-inflammatory and triglyceride-lowering properties. In particular, EPA and DHA decrease inflammation in adipose tissue and improve insulin sensitivity [135]. These fatty acids exert their antitumor activities by regulating the Wnt/β-catenin and Hippo pathways, modulating oxidative stress, and influencing the expression of granzyme B, ultimately affecting proliferation, apoptosis, and migration [135].

Fiber and whole grains

Since 2017, the WCRF has supported the view that fiber and whole grains "probably" reduce the risk of CRC. Consuming at least 10 g of fiber daily is associated with a reduction in CRC risk by up to 10% [136]. Fiber aids in increasing fecal bulk and speeding up intestinal transit, which reduces the duration that carcinogens are in contact with the intestinal mucosa [137]. Moreover, fiber helps in weight management [138] and reduces the risk of type 2 diabetes [139]. When fermented by the gut microbiota, fiber produces metabolites, such as short chain fatty acids (SCFAs), which exert anti-inflammatory and anticarcinogenic effects [140].

Whole grain cereals are a major source of dietary fiber sources and are more beneficial for human health compared to their refined counterparts produced by removing the bran and germ, resulting in lower fiber and micronutrient content [141]. Whole grains are also rich in polyphenols and flavonoids, which are antioxidants with potential anti-tumor properties [141]. Moreover, whole grains have a lower glycemic index compared to that of refined grains, which helps prevent insulin resistance and obesity [142].

Overall, whole grains act as protective factors against gastrointestinal cancers, whereas refined cereals are associated with an increased risk of CRC [141, 143]. This distinction highlights the significant impact that diet can have on the prevention and management of CRC.

Anti-inflammatory drugs

The link between nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin, and CRC has been extensively studied [144]. The chemopreventive properties of NSAIDs are mainly attributed to cyclooxygenase COX-2 inhibition, which leads to decreased tumor cell proliferation and angiogenesis by suppressing prostaglandin E2 production [145], known to promote tumor growth and development. For individuals with Lynch syndrome, a genetic condition that increases CRC risk (see Sect. "Lynch syndrome and constitutional MMR deficiency syndrome"), the administration of low-dose acetylsalicylic acid—commonly known as aspirin—ranging from 75 to 100 mg per day, is recommended to help lower their risk of developing CRC [146].

Another drug reported to have anti-inflammatory and anti-cancer properties is metformin, which is commonly used for patients with type 2 diabetes [147, 148]. Moreover,

metformin has been proposed to contrast obesity [149]. Metformin suppresses hepatic gluconeogenesis, by decreasing mitochondrial respiration and by activating Adenosine Monophosphate-Activated Protein Kinase (AMPK), and increases skeletal muscle sensitivity to insulin promoting peripheral glucose utilization. The activation of AMPK by metformin also leads to NF-κB modulation and reduced inflammation. The effects of metformin in cancer prevention are due to AMPK activation and insulin/insulin-like growth factor 1 (IGF-1) signaling downregulation, suppress cell proliferation and inflammation, and to the promotion of the immune response [147].

Gut microbiota and metabolome

The collection of microorganisms (*i.e.*, bacteria, viruses, fungi, and protozoa) colonizing the GI tract is defined as the "gut microbiota", which comprises more than 10^{14} cells [150]. This diverse microbial community is primarily made up of the phyla Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria [151]. The distribution of these microbes along the GI tract varies due to changes in the oxygen gradient [152].

In a state of equilibrium, known as eubiosis, the gut microbiota performs various beneficial functions for the host. However, this balance can be disrupted, leading to an altered microbial composition, referred to as dysbiosis [153]. Among their beneficial functions, gut microbes can ferment complex carbohydrates to produce metabolites such as SCFAs, of which propionate, butyrate, and acetate are the most abundant. These SCFAs are rapidly absorbed by epithelial cells in the GI tract where they are used as energy source and are involved in the regulation of cellular processes, such as gene expression, differentiation, chemotaxis, proliferation, and apoptosis. These metabolites also play an important role in immune system regulation and in the inflammatory response by influencing the secretion of anti-inflammatory cytokines [154].

Another important aspect of this symbiotic relationship is that the gut microbiota can synthesize vitamins for the host. For instance, lactic acid bacteria are key producers of vitamin B12, while Bifidobacteria are key producers of folate. Other vitamins like vitamin K, riboflavin, biotin, nicotinic acid, pantothenic acid, pyridoxine, and thiamine can also be synthesized by various members of the gut microbiota [155].

The presence of microbial species in the human GI tract also plays a crucial role in preventing pathogen colonization by competing for attachment sites or nutrients and by producing antimicrobial proteins. These proteins can disrupt bacterial cell walls through direct interaction and enzymatic action, effectively controlling the growth of harmful bacteria [156].

Another important function of the gut microbiota is its role in maintaining the integrity of the mucosal barrier. The GI epithelium provides a physical barrier facilitated by tight junction proteins that link with the cytoskeleton to form a complex structure, which reduces gut permeability. The intestinal epithelium also provides a chemical barrier through the outer mucus layer secreted by goblet cells of the epithelium itself. Indeed, commensal bacteria producing anti-microbial proteins are found on this intestinal epithelium, enhancing its defensive properties. In the lumen, these beneficial bacteria produce bacteriocins, modify the lumen pH, and compete for nutrients, thus preventing the colonization by pathogenic bacteria [157].

The combined physical and chemical barrier functions of the intestinal epithelium help maintain gut integrity and homeostasis. If this protective capacity is compromised, it can lead to bacterial translocation and the entry of toxic microbial products, such as pro-inflammatory endotoxins and metabolites, across the colonic epithelium [157].

A primary consequence of microbial dysbiosis is the weakening of the gut barrier, which causes a shift in microbial communities, turning otherwise commensal bacteria into potential pathogens. This weakening is often attributed to disturbances in the epithelium architecture, including the destabilization of tight junctions and increased bacterial invasiveness [157]. Such alterations may further shift in the microbiota composition, potentially causing chronic inflammation and the onset of CRC. This complex interplay highlights the critical role of a balanced gut microbiota in preserving overall GI health and preventing disease.

Bacteria associated with CRC

Gut dysbiosis is associated with different types of cancer, chiefly CRC. Specific changes in the microbiome occur during different stages of CRC progression—from adenomatous polyps to early-stage cancer to metastatic disease—underscoring the significant etiological role of the gut microbiota in CRC development [4, 158].

Several bacterial species are directly implicated in the pathogenesis of CRC. For instance, *Fusobacterium nucleatum*, *Bacteroides fragilis*, and *E. coli*, are all species found enriched in lumen-associated microbiota (LAM) or mucosa-associated microbiota (MAM) of CRC patients compared to healthy controls [159–162]. Further details on these bacteria are described in the next section.

The "driver-passenger" model

The "driver-passenger" model has been proposed to explain the interaction between bacteria and CRC development [163] (Fig. 2). This model mirrors the genetic framework where driver mutations— both genetic and epigenetic—initiate and

promote the early stages of cancer by causing epithelial dysplasia in the colon. As the cancer develops, it accumulates "passenger" mutations that do not initiate cancer but may support tumor progression once it has begun. Similarly, in the microbial context of CRC, driver bacteria are the initiators of cancer, creating conditions that lead to tumorigenesis. In contrast, passenger bacteria, while not initiators themselves, thrive in the cancerous environment and take advantage of the cellular disruptions caused by the disease, further contributing to cancer progression [163].

The pro-carcinogenic characteristics of driver bacteria include their ability to produce genotoxic compounds that damage DNA in colonic epithelial cells, stimulate the cleavage of some tumor suppressor proteins—causing cell proliferation—compromise gut barrier integrity, and induce a chronic inflammatory response that can push the colonic epithelium towards carcinogenesis [163]. Notable driver bacteria include the enterotoxigenic *B. fragilis (ETBF)* and *pks*$^+$ *E. coli* [164]. In particular, ETBF secretes the *B. fragilis* toxin, a zinc-dependent metalloprotease that targets epithelial tight junctions—leading to E-cadherin cleavage—activates the Wnt/β-catenin signaling pathway, and increases gut barrier permeability. In addition, this toxin induces colon inflammation and DNA damage [165–169], playing a significant role in CRC initiation.

Other pathogens involved in CRC carcinogenesis include particular strains of *E. coli* called *pks*$^+$ *E. coli*, which harbor the polyketide synthase gene complex (*pks*) [170], encoding colibactin, a genotoxin able to induce DNA double-strand breaks, cell cycle arrest, and chromosomal aberrations [171, 172].

In this scenario, our recent research has revealed significant differences in tumor-associated microbiota and metabolome between low-grade and high-grade dysplastic colon polyps. Specifically, high-grade dysplasia adenomas are colonized by candidate passenger genera, while low-grade dysplastic polyps show a higher presence of *B. fragilis,* underscoring the potential role of this species in initiating pre-malignant lesions [158]. Indeed, in the presence of an adenoma or carcinoma, passenger bacteria, normally poor colonizers of a healthy intestinal tract, seem to acquire the ability to breach the colon wall. This process may be ascribable to the tumor microenvironment (TME), which not only supports their proliferation but also play a role in CRC progression [163]. For example, Tjalsma and colleagues have identified *F. nucleatum* [163]—a gram-negative anaerobe bacterium that normally colonize the oral cavity and that is found in higher concentrations in CRCs compared to adjacent normal tissues—as a potential passenger bacterium. Present in approximately 10–15% of CRCs, *F. nucleatum* has been linked to advanced disease stage, poor survival rates, and increased risk of recurrence [4, 173, 174]. In addition, the presence of this species in tumor tissues is associated with decreased T-cell infiltration and reduced anti-tumor immune response [4, 175]. Interestingly, *F. nucleatum* may also act as a driver in CRC development [176]. Kostic et al. found that the introduction of *F. nucleatum* accelerated the onset of colonic tumors in mice [177], with its lipopolysaccharide activating the β-catenin and NF-κB pathways via the Toll-like receptor 4 (TLR4) cascade [176]. *F. nucleatum* is thought to drive CRC progression by means of two virulence factors: FadA, which activates the E-cadherin/β-catenin pathway in colon cancerous cells [178, 179], and Fap2, which binds to Gal-GalNAc residues, overexpressed on the surface of CRC cells and interacts with the TIGIT receptor present NK cells and various T cells, inhibiting immune cells activity [177, 180].

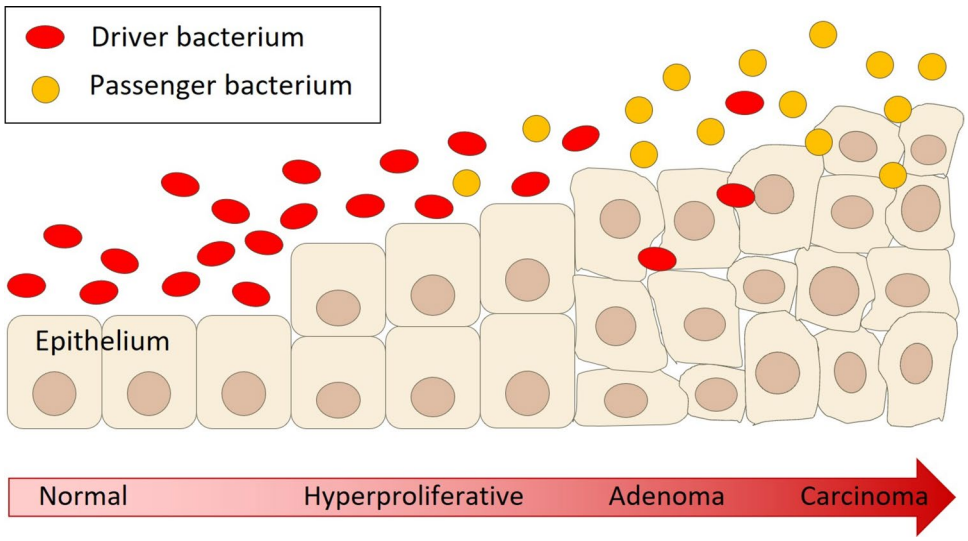

Fig. 2 Cartoon depicting the bacterial driver–passenger model for colorectal cancer

Metabolome and CRC

The gut microbiota synthesizes a large variety of metabolites, including volatile small molecules, lipids, proteins and peptides, sugars, secondary bile products or terpenoids, biogenic amines, oligosaccharides, glycolipids, organic acids, and amino acids. These metabolites can all significantly affect host physiology and contribute to the pathogenesis of various diseases [181]. Changes in the metabolite profiles are often observed alongside alterations in bacterial composition associated with CRC stage. Therefore, integrating microbiota and metabolome data can provide important insights into the role of the gut microbiota in both the production and consumption of these metabolites [158].

The comprehensive set of metabolites found in a biological sample, such as feces, biopsies, urine, or serum, is termed the metabolome. Analysis of the metabolome has identified a number of metabolic biomarkers for CRC [182]. A recently developed high-throughput metabolomics method, based on a swab-brushing procedure, has been shown to efficiently capture the metabolites adherent to adenomatous polyps and adenocarcinoma without compromising tissue integrity, crucial for subsequent histological analysis [183]. This advancement in metabolomic profiling represent a substantial step forward in our understanding of the metabolic changes associated with CRC progression and may lead to improved diagnostic and therapeutic strategies.

Short chain fatty acids

As aforementioned, SCFAs are among the most studied gut microbiota-derived metabolites due to their potential to reduce the risk of CRC. SCFAs such as propionate, butyrate, and acetate are produced through fermentation of non-absorbable dietary fibers by various members of the intestinal microbial community [184]. These fatty acids play a crucial role in modulating the immune response by reducing levels of pro-inflammatory cytokines while increasing those of anti-inflammatory cytokines and T-reg cells [4, 184], which are crucial for maintaining immune balance and preventing inflammation-driven carcinogenesis.

The production of these SCFAs varies by their location in the colon (with higher concentrations in the proximal colon) and the types of bacteria present in those areas. Members of the Bacteroidetes phylum primarily produce acetate and propionate, whereas Firmicutes mainly synthesize butyrate [164].

Butyrate has different effects on carcinogenesis according to the host genetic background. Generally, butyrate is beneficial as it upregulates the expression of pro-apoptotic and tumor-suppressor genes in cancerous colonocytes. On the other hand, in mice with germline mutations of *Apc* and MMR genes, which are critical for DNA mismatch repair and cellular growth control, butyrate has been shown to accelerate cell proliferation [185, 186]. This dual role underscores that impact of SCFAs on CRC risk may depend on both microbial and host genetic factors.

Trimethylamine N-oxide

TMAO is an important gut microbe-dependent metabolite produced after the metabolization of L-carnitine, betaine and dietary choline to trimethylamine (TMA) by the gut microbiota [184]. As previously mentioned (see Sect. "Red and processed meat"), red meat has a high content of choline and carnitine, and its consumption is therefore associated with increased levels of the pro-inflammatory metabolite TMAO [184, 187], elevating the risk of CRC.

Secondary bile acids

BAs (see Sect. "Red and processed meat") are classified as primary (e.g., cholic acid, CA), secondary (e.g., deoxycholic acid, DCA), and tertiary (e.g., taurocholic acid, TCA). Primary BAs are synthesized from cholesterol in the liver and can be metabolized by gut bacteria to generate secondary BA. Tertiary BAs are formed via hepatocyte metabolism of reabsorbed primary BAs. High levels of secondary BAs, particularly DCA, have been correlated with an increased risk of CRC [164]. DCA contributes to carcinogenesis by eliciting DNA damage in epithelial cells, leading to apoptosis. It also induces oxidative stress and activates NF-κB, promoting inflammation [188, 189].

Polyamines

Polyamines, such as spermidine, are biosynthesized from the amino acids arginine and ornithine, and they also can be derived from dietary sources or produced by both the host and the gut microbiota [190]. Spermidine, for example, can be produced by host or microbiota or ingested with diet. Enterotoxigenic *B. fragilis*, through its spermine oxidase (SMO) catalyzes the conversion of spermine to spermidine, a process that generates H_2O_2, promoting cellular oxidative stress [168].

Polyamines induce intracellular oxidative stress and DNA damage, accelerating carcinogenesis and facilitating cell proliferation and tumor metastasis [168, 184].

Conclusions

In conclusion, CRC arises from a multifactorial etiology encompassing a broad range of risk factors. These factors collectively determine the likelihood of initially developing colorectal polyps and, ultimately, carcinomas. Embracing a

healthy lifestyle, which includes a nutritious and fiber-rich diet, regular physical activity, and the avoidance of smoking and excessive alcohol consumption, can significantly mitigate the risk of CRC. Such lifestyle choices also promote intestinal eubiosis, fostering a balanced microbiome.

The insights from this review highlight the importance of understanding how these factors interact with the gut microbiome to influence the development and progression of CRC. This understanding has already enhanced, and will continue to improve, the prevention and management of CRC, both in sporadic cases and in patients with inherited cancer syndromes.

It is conceivable that in a nearby future personalized medicine will expand into gut health through custom interventions tailored to the unique microbiota profile of each individual to prevent and treat CRC. This approach may include regular screening to map an individual's intestinal microbiota and metabolome, guiding targeted dietary adjustments, the strategic use of prebiotics and probiotics, and even fecal transplant from healthy donors [191]. In addition, modifications of the intestinal microbiota could enhance the effectiveness of existing immunotherapies [192], thereby improving outcomes in CRC therapy.

This review confirms that genetics, diet, microbiota, and metabolome collaboratively act as "partners in crime" in the multifaceted development of colon carcinogenesis, underscoring the need for integrated approaches in CRC prevention and management.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

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