Review

Discovery Medicine 2025; 37(198): 1176–1199
https://doi.org/10.24976/Discov.Med.202537198.105

Emerging Role of Gut Microbiome and Risk of Developing Colorectal Cancer and Its Implications in Treatment

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Published: 20 July 2025

Colorectal cancer (CRC) represents a significant cancer type that leads to many worldwide deaths because its occurrence keeps rising in specific demographic groups. Three elements affect CRC development: genetic makeup, in addition to environmental variables and disturbances in the gut microbiome population. Research now demonstrates that dysbiosis, which is an irregularity in gut microbial populations, plays a fundamental role in stimulating colorectal cancer formation and its advancement. Three bacterial types, namely *Fusobacterium nucleatum*, *Escherichia coli*, and *Bacteroides fragilis*, act as carcinogenic agents in the body by generating chronic inflammation conditions, causing DNA damage and impairing immune defenses. The composition of gut microbiota experiencing modifications due to lifestyle elements like diet and obesity, together with smoking habits and alcohol consumption, ultimately impacts CRC development. Scientific discoveries in the field of microbiome research now enable better opportunities for the prevention and early detection of CRC. Scientists identify microbial biomarkers as potential tools for creating non-invasive testing methods that could fulfill upcoming screening needs. Scientists are currently examining microbiota-targeted treatments like probiotics alongside prebiotics and dietary interventions and also consider fecal microbiota transplantation (FMT) for both CRC prevention and management approaches. The specific treatments intend to rebuild correct gut bacterial levels while promoting beneficial microbial activity alongside lowering inflammatory pathways that contribute to tumor development. A detailed analysis of CRC-gut microbiota associations occurs in this review through investigations about carcinogenic bacterial species plus their pathways, along with environmental factor impacts. The review explores diagnostic methods and treatment possibilities based on microbiome research for managing CRC. Progress in gut microbiota allows potential development of personalized prevention and treatment methods, which hold promise to lower global colorectal cancer incidents.

Keywords: colorectal cancer; dysbiosis; gut microbiome; *Fusobacterium nucleatum*; *Escherichia coli*; *Bacteroides fragilis*

Introduction

Colorectal cancer (CRC) stands as a significant global cancer type that constitutes an important health challenge worldwide. Worldwide statistics show CRC as the third most common cancer by occurrence rates and the second leading cause of cancer-related deaths in 2021 [1]. Research shows CRC cases will increase to 3.2 million in 2040 [2]. CRC incidence and mortality rates decreased consistently for people aged 65 and above during the past decades because more patients underwent colonoscopy screenings [3]. A worrying pattern has emerged regarding CRC incidence among younger adults as their cases continue to increase. The number of colon cancer instances grew by 2.4% per year in people aged 20 to 29 years and by 1.0% per year in people aged 30 to 39 years and by 1.3% per year in adults aged 40 to 49 during the period from the mid-1980s to 2013 in the United States [4]. The age group of 50–54 experienced a 0.5% annual increase in incidence starting from the mid-1990s. The increasing health challenges faced by younger adults emphasize the pressing requirement to create better methods for preventing and detecting CRC early [5].

A combination of genetic elements together with environmental influences controls CRC development. The majority of CRC cases develop sporadically because most patients do not inherit genetic predispositions yet three specific inherited conditions including Familial Adenomatous Polyposis (FAP) and Lynch syndrome and Peutz-Jeghers syndrome collectively account for a small number of cases

[6]. The development of sporadic CRC depends heavily on environmental factors that encompass Westernized eating patterns and obesity together with smoking habits and diabetes control, and heavy alcohol use [2,7]. The gut microbiota has become a central focus of scientific inquiry among these factors.

Research indicates that the human intestinal microbiota contains 10–100 trillion microbial cells, which surpass human cells by almost tenfold in number [8]. The numerous bacteria present in the human intestinal system contain more than 100 times as many genetic elements as found in human DNA. The presence of healthy gut microbiota plays a vital role in maintaining energy metabolism and supporting intestinal epithelial health and immune system functions, and serves as protection against pathogens [9]. Dysbiosis, which represents an imbalance in gut microbial balance, leads to various diseases, including CRC, because it affects host physiology negatively [10].

Scientists have researched the relationship between gut microbiota and colorectal carcinogenesis through studies that show different microbial compositions exist between CRC patients and people without the condition [11–13]. Medical research shows specific bacterial populations either increase or decrease in CRC patients with similar alterations observed in individuals who have colorectal adenomas, which precede CRC development [13]. Research shows that changes in gut microbiome may serve as valuable biomarkers for diagnosing CRC at early stages of its onset. Specific microbial signatures such as *Fusobacterium nucleatum*, *Bacteroides fragilis*, and polyketide synthase positive (pks+) *Escherichia coli*, which are linked to CRC progression, have been identified through metagenomic and metabolomic analyses and may act as precursors for early diagnosis [14]. These microbes have been shown in studies to aid in tumor formation through inflammatory and genotoxic processes, indicating their importance as diagnostic markers. Furthermore, older studies conducted in the 1960s proved that dietary carcinogen cycasin caused cancer in conventional rats but not in germ-free rats, highlighting the role of the microbiome in carcinogen activation [15]. Studies on Campylobacter species, particularly *C. jejuni* and *C. concisus*, over the last twenty years have further demonstrated a possible association of bacterial infection with CRC pathology by epithelial breach and immune evasion [16]. There is also support for the view that changing gut microbiota by diet, probiotics, prebiotics, or fecal microbiota transplantation (FMT) can be an effective method for both prevention and treatment of CRC. Together, these results underline the necessity of further studies on microbome-based diagnostics and therapies aimed at realizing better results for CRC patients.

The review analyzes modern research data from animal and human studies about how gut microbiota contributes to CRC development. It also looks at the mechanisms of tumorigenesis while analyzing new approaches for CRC prevention and therapy through modulation of the microbiome.

Correlation Between CRC and Gut Microbiome

Scientists predict that the rising use of Western dietary patterns globally will lead to increased colorectal cancer (CRC) cases reaching 2.2 million new diagnoses by 2030 [2]. It has been reported that CRC develops spontaneously in 90% of cases, yet the other 10% stem from inherited genes and particular environmental triggers [17]. The development of CRC depends heavily on major lifestyle choices, including physical inactivity together with smoking and Western diet consumption and low fiber intake and alcohol use, and obesity. Several environmental factors that contribute to CRC risk modify the composition of gut microbiota [18].

Several studies confirm that gut microbiome shifts play a role in both CRC development and tumor evolution through inflammatory mechanisms and DNA damage processes, and microbial metabolite production effects on cellular operations [19–22]. Advanced microbiome sequencing technologies enabled scientists to study the relationship between gut microbiota and host health and its influence on CRC development. Earlier research has analyzed microbe populations between cancerous colon tissue and healthy tissue to identify variations between patients who have CRC and those who do not [12].

CRC patients demonstrate reduced gut microbiota diversity together with lower richness when compared to healthy individuals [23,24]. CRC cases exhibit noteworthy microbial composition changes, which potentially distort the mucosal immune response more strongly in cancer patients [25]. Eleven microbial communities that thrive more frequently in patients with CRC among the Enterococcus, Escherichia/Shigella, Klebsiella, Streptococcus, and *Peptostreptococcus* groups have been discovered. The number of beneficial bacteria Roseburia and butyrate-producing species from the *Lachnospiraceae* family decreased significantly [26].

The gut microbiota of CRC patients shows dysbiosis because their microbial populations become imbalanced. The combination of microbial imbalance and increased intestinal permeability produces colonic inflammation that advances CRC development [27]. The presence of *Fusobacterium nucleatum* (*F. nucleatum*) occurs at higher levels among CRC patients than among people without cancer [28]. Composition of gut microbiome differs between CRC that has progressed to advanced adenoma and definitive CRC stages [11]. CRC exists in a direct correlation with the gut microbiome composition [29] (Table 1, Ref. [13,30–34]). Additional investigations to determine precisely how gut bacteria affect the beginning and evolution of CRC need further investigation.

Table 1. Key gut microbiota factors and their impact on colorectal cancer (CRC).

Factor	Impact on CRC Development	Microbial Associations	References
Western Diet & Lifestyle	Increases CRC risk through inflammation, obesity, and metabolic changes.	Alters gut microbiota, reducing beneficial bacteria and increasing pathogenic strains.	[30]
Gut Microbiota Diversity	CRC patients exhibit lower microbial diversity, affecting immune response.	Beneficial bacteria (*Roseburia*, *Lachnospiraceae*) are reduced; harmful bacteria (*Enterococcus*, *Klebsiella*, *Streptococcus*) are increased.	[31]
Dysbiosis & CRC Progression	Imbalance in gut microbiota leads to increased intestinal permeability and inflammation.	*Fusobacterium nucleatum* is more abundant in CRC patients, influencing tumor growth and metastasis.	[13]
Inflammation & DNA Damage	Chronic inflammation leads to genetic mutations and tumor progression.	Pathogenic bacteria (*Escherichia/Shigella*, *Peptostreptococcus*) produce toxins that damage DNA.	[32]
Metabolic Changes & CRC Risk	Microbial metabolites influence cell proliferation, apoptosis, and tumor growth.	Butyrate-producing bacteria (*Lachnospiraceae*) decrease, while pro-inflammatory metabolites from *Bacteroides fragilis* increase.	[33]
Early vs. Late-Stage CRC	Gut microbiota composition differs between adenomas and advanced CRC.	*F. nucleatum* and *Escherichia coli* are more prevalent in later-stage disease.	[34]

F. nucleatum, *Fusobacterium nucleatum*.

Intestinal Microbiota and Colorectal Cancer

The human intestine contains a large collection of microorganisms that establish a beneficial partnership with intestinal cells to establish a necessary stable gut environment and the disruption of this balance results in different intestinal disorders, which may include colorectal cancer (CRC) [35]. During the 1960s, scientists discovered that Cycas acted as a carcinogenic agent toward conventional rats but did not cause cancer in germ-free rats [36]. It has been reported that intestinal microorganisms play essential roles in developing Cycas-induced cancers [37]. A case-control investigation of CRC patients has been conducted to examine fecal microbiota patterns together with inflammatory markers across benign polyp and advanced adenoma stages of tumour development [38]. Research has identified 24 bacteria types linked to CRC while demonstrating that tumour microenvironment changes through disease progression depend on bacterial makeup [39]. CRC develops mainly because of four main bacteria groups: *Fusobacterium nucleatum*, *Escherichia coli*, *Bacteroides fragilis*, and *Campylobacter jejuni* [40]. The Fig. 1 shows bacterial species that cause DNA damage and inflammation, together with their specific mechanisms.

Fusobacterium nucleatum: The anaerobic Gram-negative bacterium *Fusobacterium nucleatum* exists naturally in human oral cavities, through which it facilitates the development of periodontal disease by linking diverse microbial species in biofilm structures. Multiple stages of CRC development are influenced by the bacterium *F. nucleatum*according to mounting scientific evidence [41].

The bacteria drive cancer cell growth by using these two systems:

(a) The Wingless-related integration site (Wnt)/β-catenin signaling pathway, essential for CRC progression, becomes activated through Fusobacterium adhesion A (FadA) protein binding to E-cadherin on host cells [42].

(b) The activation of Toll-like receptor 4 (TLR4) and Transcription factor-κB (NF-κB) enhances microRNA-21 (miR-21) production, while this microRNA is known for its role in cancer development [43].

The study of Apcmin/+ mice showed that *F. nucleatum* enhances both cancer cell multiplication and inflammatory reactions, which leads to faster tumor development. The bacterium helps cancer metastasis through its interactions with microbial species, including *Bacteroides*, as well as *Selenomonas* and *Prevotella* [44,45]. The bacterium has been found in both CRC metastases that spread to the liver and in lymph node regions [45,46]. It has been reported that *F. nucleatum* plays a role in both preventing cancer cells from resisting chemotherapy treatments and leading to tumor regrowth. The bacterium blocks autophagy-regulating microRNA molecules (miR-18a* and miR-4802), which hinders the success of cancer treatment. The microorganism increases glycolysis function, which supports cancer cell survival through its ability to modify histones and regulate Enolase 1 (ENO1) enzyme expression [47].

Escherichia coli

The human intestine receives its first Gram-negative bacteria colonizer, *Escherichia coli* (*E. coli*), right after birth [48]. The majority of *E. coli* strains are not harmful, but specific virulent strains have the ability to trigger gas-

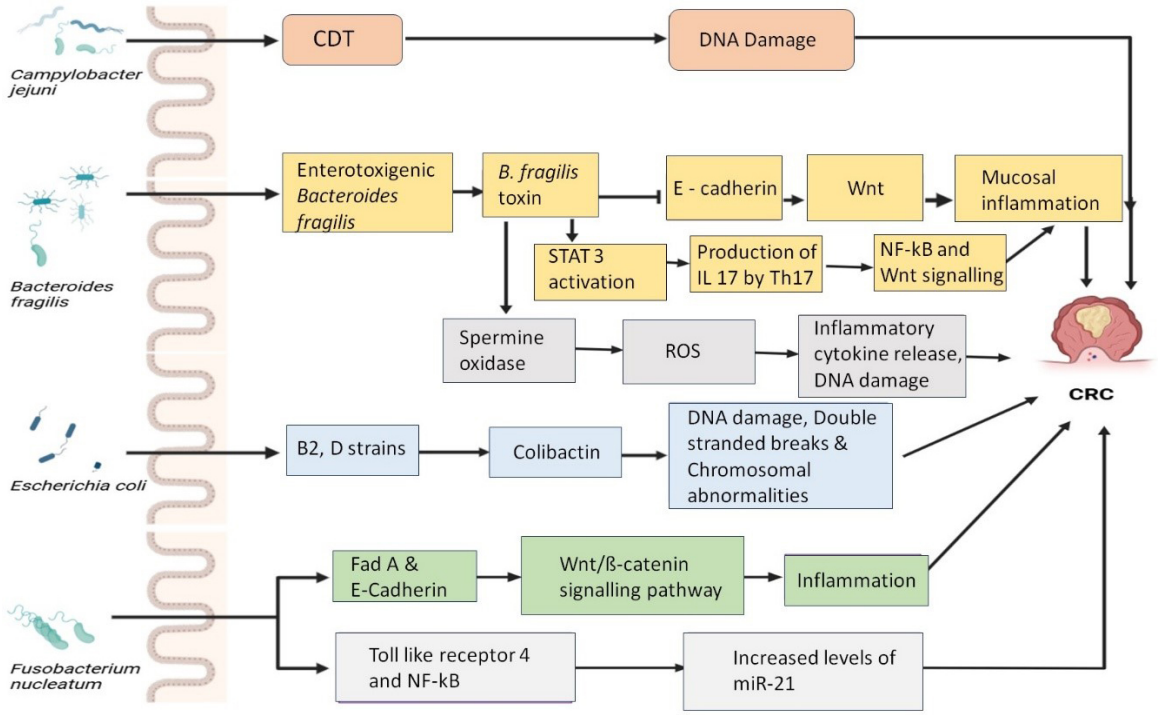

Fig. 1. Mechanisms of Bacterial-Induced DNA Damage and Inflammation. *Fusobacterium nucleatum*: Stimulates CRC through Wnt/β-catenin stimulation (Fusobacterium adhesion A (FadA)-E-cadherin) and TLR4/NF-κB-mediated miR-21 synthesis. Improves tumor growth, metastasis, chemotherapy resistance, and glycolysis. *Escherichia coli*: Pathogenic B2/D strains are reported to synthesize colibactin, thereby causing DNA damage and mutations that propel CRC forward. *Bacteroides fragilis*: Enterotoxigenic *Bacteroides fragilis* (ETBF) produces *Bacteroides fragilis* toxin (BFT) and blocks E-cadherin, which, by augmenting the Wnt/STAT3/IL-17 signaling pathway and ROS, results in CRC. *Campylobacter jejuni*: CDT toxins induce DNA lesions; in collaboration with *C. jejuni*, promotes tumor growth in Apcmin/+ mice, thus associating *C. jejuni* with CRC. Biorender software (https://www.biorender.com/) was used to create the figure. CRC, colorectal cancer; TLR4, Toll-like receptor 4; NF-κB, Transcription factor-κB; STAT3, signal transducer and activator of transcription-3; ROS, reactive oxygen species; IL-17, Interleukin 17; CDT, cytolethal distending toxin; Wnt, Wingless-related integration site; Th17, T helper 17; miR-21, microRNA-21.

trointestinal diseases [49,50]. Pathogenic strains responsible for CRC primarily belong to groups B2 and D of *E. coli* bacteria, while these strains also represent Inflammatory bowel disease (IBD) strains that function as known risk factors for CRC [51]. The toxin responsible for CRC development by *E. coli* was identified in 2006 as colibactin. The DNA-damaging effects of colibactin, along with double-strand breaks and chromosomal abnormalities, drive CRC development [52]. The presence of colibactin-producing *E. coli* cells in mice models enhances the speed of colon cancer development [53]. The DNA regions containing adenine-thymine (AT) sequences in human CRC cells represent the primary targets for colibactin, which enhances the likelihood of mutations occurring [54]. A vast cancer genome studied by researchers shows that colibactin generates numerous mutations, which occur frequently in CRC cases [55].

Bacteroides fragilis

The gut bacterium *Bacteroides fragilis* exists commonly in the human body while supporting digestion functions and intestinal health [56]. Enterotoxigenic *Bacteroides fragilis* (ETBF) stands as a particular strain of *Bacteroides fragilis,* which generates *Bacteroides fragilis* toxin (BFT) that links to CRC development. BFT functions as a toxin that breaks down E-cadherin protein, which holds cells together inside the intestinal epithelial barrier. The Wnt signaling pathway gets activated after this process, which functions as a primary factor in colorectal tumorigenesis [57–59]. ETBF activates inflammatory responses in mucosa while simultaneously generating conditions that make tumors thrive. The transformation process focuses on the signal transducer and activator of transcription-3 (STAT3) pathway because it functions as a vital regulator of immune responses. The activation of STAT3 follows ETBF exposure to produce Interleukin 17 (IL-17) through T helper 17 (Th17) immune cells [60]. Wnt signaling and NF-κB signaling become more active due to this effect, which

Table 2. Bacterial species implicated in colorectal cancer (CRC).

Bacterium	Characteristics	Mechanisms of CRC Promotion	Key Studies & Findings	References
Fusobacterium nucleatum	Anaerobic, Gram-negative, found in the oral cavity	- Activates Wnt/β-catenin signaling via FadA-E-cadherin interaction - Induces NF-κB and miR-21 via TLR4 activation - Enhances glycolysis and histone modifications - Contributes to chemotherapy resistance and metastasis	- Present in CRC metastases (liver, lymph nodes) - Accelerates tumor growth in Apcmin/+ mice - Reduces treatment effectiveness by inhibiting miRNAs involved in autophagy	[65]
Escherichia coli	Gram-negative, intestinal colonizer, includes virulent strains from B2 and D groups	- Produces colibactin, causing DNA damage and double-strand breaks - Targets AT-rich DNA regions, increasing mutation risk	- Colibactin-producing *E. coli* accelerates CRC in mice - Colibactin-associated mutations found in human CRC genomes	[66]
Bacteroides fragilis	Common gut bacterium; enterotoxigenic *Bacteroides fragilis* (ETBF) produces *Bacteroides fragilis* toxin (BFT)	- BFT cleaves E-cadherin, activating Wnt signaling - Induces STAT3 activation, promoting IL-17-driven inflammation - Increases reactive oxygen species (ROS) via spermine oxidase (SMO)	- IL-17 inhibition reduces CRC in mice - ETBF enhances NF-κB and Wnt signaling, fueling CRC progression	[67]
Campylobacter jejuni	Gram-negative, produces cytolethal distending toxin (CDT)	- CDT causes DNA double-strand breaks, leading to genomic instability - Alters gut microbiota composition - Increases tumor size and number in Apcmin/+ mice	- CDT-deficient strains show reduced tumor formation - Germ-free mice colonized with *C. jejuni* exhibit increased tumor burden	[63]

This table summarizes key bacterial species associated with CRC, highlighting their characteristics, mechanisms of carcinogenesis, and significant research findings.
TLR4, Toll-like receptor 4; NF-κB, Transcription factor-κB; STAT3, signal transducer and activator of transcription-3; IL-17, Interleukin 17; AT, adenine-thymine; *E. coli*, *Escherichia coli*.

advances the development of CRC [61]. Research with mice indicated that blocking IL-17 reduces tumor development. ETBF stimulates colonic epithelial cells to increase spermine oxidase (SMO) expression, which results in higher reactive oxygen species (ROS) production. The combination of inflammatory cytokines and DNA damage and CRC progression occurs as a result of these events [62].

Campylobacter jejuni

The investigation of Campylobacter species, including *C. jejuni,* for CRC development started more than twenty years ago. The bacterium generates cytolethal distending toxin (CDT) that possesses Deoxyribonuclease (DNase) activity to cause DNA double-strand breaks. Apcmin/+ mice without germs developed bigger and more tumors after *C. jejuni* colonization, which altered their gut microbial community structure [63]. The absence of the Clostridium difficile transferase B subunit (CDTb) in a *C. jejuni* mutant strain resulted in impaired CDT production and consequently diminished tumor formation together with decreased DNA damage. *C. jejuni* uses CDT as a key factor to enable cancer development [64] (Table 2, Ref. [63,65–67]).

Microbial Differences Across CRC Subtypes and Location

CRC is a disease capable of biological diversities consisting of several subtypes which possess different genetic, epigenetic, and clinical characteristics [68]. There is mounting evidence indicating that these subtypes may also have unique compositions of gut microbiota that could affect tumorigenesis, disease progression, and response to treatment [69]. Despite the increasing information, there lack of sufficient literature on the associations between various CRC subtypes and the microbial communities they harbour. A more in-depth examination of microbiota differences between CRC subtypes may help decipher the impact of the microbiome in disease mechanisms and treatment.

Molecular Subtypes and Microbiota Associations

Microsatellite Instability-High (MSI-H) CRC

MSI-H tumors are known to possess an abundance of *Fusobacterium nucleatum* (Fn) due to its defective DNA mismatch repair [70]. Such a bacterium is known to boost immune evasion through host immune modulation, T-cell depletion, and Programmed Death-Ligand 1 (PD-L1) immune checkpoint overexpression. Additionally, infection with Fn has also been linked to chemotherapy resistance in MSI-H tumors as a result of worsened prognosis due to fluoropyrimidine chemotherapy and immunotherapy [71]. Given the overabundance of Fn in MSI-H tumors, it is plausible that these bacteria help shape the tumor microenvironment and have an impact on the prognosis of patients.

Microsatellite Stable (MSS) and Chromosomal Instability (CIN) CRC

The enormous number of CRC cases is MSS with chromosomal instability often correlated with distinct gut microbiota [72]. MSS tumors are often overrepresented in *Bacteroides fragilis* and *Escherichia coli* strains possessing the pks genomic island, which synthesizes colibactin - a genotoxin capable of inflicting DNA damage leading to the advancement of tumors [73]. Besides, *Porphyromonas* and *Parvimonas* species have also been found to be within increased abundance in MSS tumors, which means that inflammatory pathways driven by microbes may have a role in the carcinogenesis of this subtype [74].

CpG Island Methylator Phenotype (CIMP) CRC

This is a hypermethylation subtype of MSS CRC tumors that CIMP may have certain signature microbes [75]. CIMP positive tumors were found to have a higher frequency of Helicobacter pylori and sulfate-reducing bacteria, suggesting a microbial link that induces epigenetic changes that facilitate tumor formation [76]. The relationship between gut microbes and patterns of DNA methylation is still being studied with possible consequences for the development of screening and intervention strategies.

Anatomic Subtypes and Microbial Differences

Apart from molecular features, there are other differences that also correlate with the location of the tumor or the anatomic subtype of the CRC [77]. For instance, proximal and distal CRCs appear to have diverse microbiomes associated with them, which may correspond to the reason for the variation in certain clinical characteristics and response to treatment [78].

Right-Sided CRC (Proximal Colon) Anomaly

Right-sided tumors develop in the cecum and ascending colon, which are microbiologically rich and less aerobic in nature [79]. The tumors are interlinked with higher proportions of the genus *Fusobacterium*, *Peptostreptococcus,* and *Prevotella,* which are known to cause inflammation and immunomodulation [80]. Inflammation of right-sided CRCs is likely to worsen prognosis in these cancers and explain the low rates of response to chemotherapy.

Left-Sided CRC (Distal Colon and Rectum)

Left-sided tumors, which occur in the descending colon, sigmoid colon, and rectum, have a different microbial biota that is often impoverished in Bacteroides and Clostridium [81]. These bacteria are known to impact the metabolism of bile acids, control inflammation, and influence tumor development [82]. The observed difference in the response of left-sided CRCs to chemotherapy and targeted therapies may be attributable to the distinct microbiota composition contributing to these tumors.

These research findings relate to how we understand the microbial composition of different CRC subtypes, which has important clinical implications. Microbiota-based biomarkers can be relevant to CRC for early identification, risk assessment, and even tailoring treatment approaches. For example, the presence of *Fusobacterium nucleatum* in MSI-H tumors indicates a prime target for alteration by immunotherapy, while the presence of pks+ *E. coli* in MSS tumors may provide new targets to lessen genomic instability associated with tumors.

Mechanisms of Intestinal Microbiota in Promoting Colorectal Cancer

Studies now emphasize the essential role of microbial communities in colorectal cancer (CRC) disease progression. The microbiome starts cancer development through inflammatory processes as well as modifying essential signaling pathways [83]. Bacterial biomarkers help both CRC detection and outcome prediction, which makes them useful for prognosis. The development of CRC depends heavily on the dynamic relationship between gut microbiome and tumor microbiome and the immune system [84]. A state of eubiosis in the gut is characterized when microbiome bacteria that exist in diverse populations while maintaining stable immune responses and controlled inflammation, and healthy mucosal barriers. The balance between gut microbiota and host cells, known as eubiosis, becomes dysbiosis when disrupted, which leads to both impaired immune responses and decreased treatment effectiveness of chemotherapy and immunotherapy [85]. Table 3 (Ref. [69,86–91]) presents an organized overview of how the gut microbiome influences CRC by describing bacterial contributions along with their mechanisms and implications, and suitable prevention and treatment approaches.

Bacterial Strains Associated With CRC

The microorganisms present in the digestive tract vary between individuals with no cancer and those suffering from CRC [92]. Various bacterial strains, such as *Bacteroides fragilis* [93], *Streptococcus gallolyticus* [94], *Enterococcus faecalis* [95,96], and *Escherichia coli* have been directly associated with CRC development. The bacterial strains *Fusobacterium nucleatum*, *Parvimonas*, *Peptostreptococcus*, *Porphyromonas,* and *Prevotella* demonstrate increased abundance in both fecal matter and tumor samples of patients who suffer from CRC [97]. The carcinogenesis process results from bacterial activities, including inflammation and immune response alteration, and harmful metabolite and genotoxin production [98].

CRC-associated bacteria fall into two groups: driver bacteria directly cause cancer, while passenger bacteria survive within tumor microenvironments [86]. The cancer-promoting signaling pathways become activated through host-microbe interactions, which eventually cause molecular changes that result in CRC progression [42]. The mechanisms studied can lead to the creation of both preventive and therapeutic interventions.

The Link Between the Microbiome and Colorectal Adenomas

Medical research has examined colorectal adenomas because they transform into cancer of the colon while studying their connection to gut microbiota. The bacterial strains *Fusobacterium nucleatum* and *Solobacterium moorei* appear in both early-stage and metastatic CRC, but the bacteria *Atopobium parvulum* and *Actinomyces odontolyticus* mainly exist in adenomas [99,100]. Study of these microbiome changes holds potential for both preventing and detecting CRC at early stages. Ahn *et al*. [22] demonstrated that CRC patients showed higher levels of *Bacteroides*, *Fusobacterium*, *Atopobium*, and *Porphyromonas* bacteria together with decreased amounts of *Firmicutes*. Therefore, mentioned a significant drawback because it examined solely fecal samples without including mucosal-adherent bacteria, which scientists believe directly affect CRC development. Additional studies should work to enhance both diagnostic techniques and prevention programs.

Mechanisms of Bacterial Influence on CRC

Bacterial species use different methods to promote colorectal cancer development. The cancer progression process occurs when *Fusobacterium nucleatum* both activates inflammatory signaling pathways and stops cellular death. The tumor environment changes due to *Peptostreptococcus,* which enhances acidity levels and enables bacterial settlement. The genotoxin-producing *Escherichia coli* strain, among others, generates DNA-damaging substances which elevate cancer development risks [101–103].

Bacterial byproducts that emerge from metabolic processes affect how the immune system functions while simultaneously influencing tumor expansion. The secreted proteins or secretomes of microorganisms contain growth factors and cytokines as well as enzymes that affect cancer cells [104]. The cancer progression process depends on microbial metabolites, which either boost tumor growth or work to suppress it. The anti-inflammatory and tumor-suppressive compound butyrate functions differently from the cancer cell growth-promoting compound lactic acid [105].

The gut microbiome is vital for colorectal cancer (CRC) development through its regulation of immune reactions and inflammatory responses, and carcinogenic processes. The healthy state of microbiome eubiosis maintains immune control and protects against CRC development, while dysbiosis leads to inflammatory responses that cause DNA damage and tumor advancement [13]. The Fig. 2 demonstrates the complex relationship between microbial equilibrium and CRC risk development and disease advancement.

Table 3. Role of gut microbiota in colorectal cancer (CRC).

Aspect	Key Findings	Implications	References
Microbiome and CRC Development	Gut microbiota influence CRC through inflammation, immune modulation, and metabolic interactions. Bacterial biomarkers aid in early detection and prognosis.	Understanding microbiome changes can help develop diagnostic and therapeutic strategies.	[69]
Bacterial Strains in CRC	Driver bacteria (e.g., *Bacteroides fragilis*, *Escherichia coli*) directly contribute to carcinogenesis, while passenger bacteria (e.g., *Fusobacterium nucleatum*, *Peptostreptococcus*) thrive in tumors.	Differentiating between driver and passenger bacteria can improve targeted interventions.	[86]
Microbiome and Colorectal Adenomas	Certain bacteria (e.g., *Fusobacterium nucleatum*, Solobacterium moorei) are linked to both adenomas and CRC.	Early detection of these bacteria could help prevent CRC progression.	[87]
Mechanisms of Bacterial Influence on CRC	Bacteria promote CRC through inflammation, DNA damage, immune suppression, and metabolic alterations.	Targeting bacterial mechanisms could lead to new CRC treatments.	[88]
Tumor Location and the Microbiome	Right- and left-sided CRCs differ in bacterial composition, genetic mutations, and immune response.	Personalized treatment approaches can be developed based on tumor location and microbiome interactions.	[89]
Diet, Gut Microbiome, and CRC Risk	High-fiber diets support beneficial bacteria, while processed foods and red meats increase CRC risk.	Dietary modifications can help lower CRC risk by maintaining a balanced microbiome.	[90]
Obesity, Gut Microbiota, and CRC	Obesity alters gut microbiota, increasing inflammation and cancer-related metabolites.	Weight management and microbiome-targeted therapies may reduce CRC risk.	[91]

The Impact of Diet on the Gut Microbiome and CRC Risk

The gut microbiome takes its shape from diet consumption and affects CRC risk levels. The microbiota helps break down food while extracting body-unavailable nutrients from food substances [106]. People who eat excessive processed food together with refined sugars and fats increase their chances of developing CRC [107]. Consuming fiber-rich foods supports healthy gut bacterial growth, leading to the production of butyrate, which helps stop tumor development. Processed red meats contain substances that harm intestinal cells while simultaneously increasing cancer development risk. The formation of dangerous substances through frying or prolonged heating of food leads to gut inflammation and increases the risk of CRC development [108,109].

Diets high in fiber, especially those abundant in fruits, vegetables, and whole grains, encourage the growth of beneficial bacteria such as *Bifidobacterium* and *Lactobacillus*, which synthesize short-chain fatty acids (SCFAs) like butyrate [110]. Butyrate is a type of SCFA that has anti-inflammatory and tumor-suppressive effects, improving the function of the gut barrier as well as the immune response. In contrast, diets high in red and processed meat consumption have been associated with an increased abundance of bacteria such as *Fusobacterium nucleatum* and *Bacteroides fragilis*, which are linked to inflammation and CRC progression [42]. Foods containing polyphenols, including berries, green tea, and dark chocolate, promote the growth of *Akkermansia muciniphila*, a gut bacterium that is known for maintaining gut health and is associated with lower CRC risk [111]. In addition, omega-3 fatty acids from fatty fish and flaxseed have been shown to increase the population of *Faecalibacterium prausnitzii*, which are important producers of anti-inflammatory SCFAs [112]. However, diets rich in fats and of western style tend to favor the growth of microbial communities, which include *Bilophila wadsworthia*, bile acid metabolizing bacteria that may induce gut inflammation and cancer [113]. Changing dietary habits, such as increasing daily fiber intake or polyphenol-rich foods while reducing processed meat consumption, can help in changing some gut microbiota composition, which would lower CRC risk [114]. These insights, along with their microbial interactions, would shed light on how to prevent CRC.

Obesity, Gut Microbiota, and CRC

The established risk factor of obesity for CRC develops through mechanisms that include insulin signaling along with inflammation and hormonal imbalances [115]. Microorganisms residing in the gut participate in cancer-related processes through modifications of inflammatory substances and cancer-causing chemical production [116].

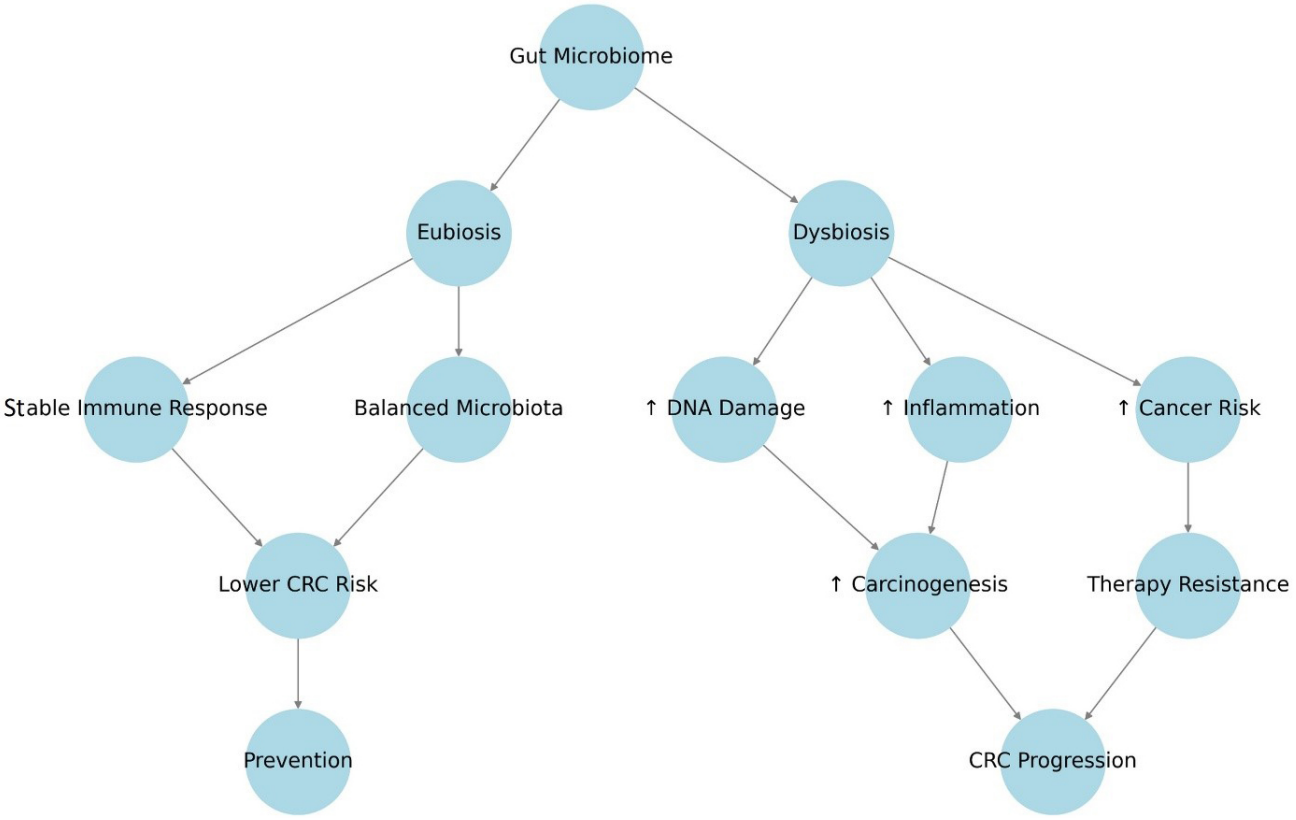

Fig. 2. The Role of the Gut Microbiome in Colorectal Cancer Progression. Bacteria promote CRC through inflammation, damaging DNA, and producing metabolic byproducts. Fusobacterium nucleatum stimulates signaling and blocks apoptosis, *Peptostreptococcus* modifies pH, and Escherichia coli causes genotoxic damage. Microbial metabolites contribute to tumor growth, and inflammation alongside dysbiosis contribute to the advancement of CRC. Biorender software (https://www.biorender.com/) was used to create the figure. Arrows mean raised or increased.

The composition of gut microbes decreases while microbial variety decreases as a result of obesity. Cancer risk decreases when individuals maintain their weight because it leads to better gut health function [117,118].

Like many microorganisms within the gut microbiome, gut bacteria have a positive and negative correlation with obesity [119]. Obese people generally have greater amounts of harmful pro-inflammatory bacteria like *Fusobacterium nucleatum*, *Escherichia coli*, and Bilophila wadsworthia [120]. On the other hand, positive gut bacteria such as Bifidobacterium and Faecalibacterium prausnitzii are significantly lower in comparison. Such microbial changes cause the creation of pro-inflammatory metabolites to increase, including secondary bile acids and lipopolysaccharides [121]. These two are known to further exacerbate inflammation together with damage to the intestines, and help the progression of CRC. Furthermore, negative metabolic changes associated with obesity, such as heightened insulin resistance and changes in fat tissue, also activate the tumor-promoting mechanisms [122]. Such data suggest that dietary habit intervention, probiotics, and prebiotics may be put in place in the future to combat obesity related dysbiosis targeting CRC. More attention is needed to specifically tackle the gap concerning personalized therapies for people with obesity, aiming to decrease the risk of CRC by restoring the microbiota composition and controlling the inflammatory response.

Mechanisms of Intestinal Microbiota in Promoting Colorectal Cancer

Disruption of Intestinal Microbiota Balance

The gut ecosystem becomes unstable when intestinal microbiota composition and structure change [123]. The decrease of beneficial bacteria alongside the rise of pathogenic bacteria both lead to colorectal cancer (CRC) development [124]. The harmful microorganisms release toxins, which cause epithelial cell damage and induce chronic inflammation while secreting these toxic substances [125]. The inflammatory process activates key signalling pathways, including NF-κB and STAT3, and Wnt/β-catenin, which promote tumor formation. Bacterial toxins damage DNA structures, which generate genetic mutations that support cancer advancement [126,127].

Role of Intestinal Microbiota in Immune Response

The intestinal microbiota regulates the development and controls both mucosal and systemic immune systems. The interaction between specific bacteria and immune cells results in the modification of immune responses through their contact with innate and adaptive immune cells, such as macrophages and pattern recognition receptors, and T cells and B cells [128,129]. The bacteria *Enterococcus faecalis* activate immune responses, which lead to CRC development through inflammatory reactions. B cells in adaptive immunity detect tumor antigens through help from CD4+ T cells to generate protective antibodies. The immune response is modulated by T and B cells through their IgA secretion, which also affects the composition of gut microbiota [130,131].

A number of bacterial species like *Bacteroides fragilis, Escherichia coli*, and *Fusobacterium nucleatum* have different approaches to immune suppression, inflammation, and tumor development [132]. *Fusobacterium nucleatum* has been associated with immune checkpoint control with special reference to upregulation of PD-L1 on tumor and immune cells [133]. *F. nucleatum* interacts with tumor-infiltrating myeloid cells through its adhesion molecule Fap2. This interaction leads to T cell suppression and subsequently, immune evasion and tumor progression. This species also suppresses anti-tumor immune activity by drawing in myeloid-derived suppressor cells (MDSCs) and blocking access to cytotoxic T cells.

Some *E. coli* strains, especially those with the pks genomic island, are known to produce the genotoxin colibactin, which damages DNA and sustains an inflammatory tumor microenvironment [134]. This environment is further nurtured by the secretion of IL-6 and IL-1β, the pro-inflammatory cytokines that promote tumor development and alter the profile of infiltrating immune cells. pks+ *E. coli* may also alter the balance of cytokines produced by macrophages towards the tumor-associated immune suppressive phenotype [135].

The enterotoxigenic strains of *Bacteroides fragilis* play a crucial role in the development of inflammation associated with CRC [136]. B. fragilis releases BFT, which is involved in the activation of the STAT3 and NF-κB pathways, leading to elevated levels of IL-17, IL-6, and tumor necrosis factor alpha (TNF-α) [67]. The IL-17 cytokine especially stimulates cell processes that cause inflammation which enabling tumor development, and B. fragilis induced T-cell differentiation and activity. On the other hand, the inflammation caused by B. fragilis may also upregulate the expression of PD-L1 in immune and epithelial cells, resulting in some degree of immune evasion.

The relationships between microbes associated with colon cancer and immune responses present an opportunity for the development of microbiome-based therapies aimed at improving immunotherapy outcomes. These results provide fresh directions for the treatment and understanding of colon cancer by unmasking the role of these bacteria in immune evasion through checkpoint modulation, T-cell infiltration, and cytokine production.

Impact on Immune Signalling Pathways

The presence of Inflammatory bowel disease (IBD) types, ulcerative colitis and Crohn's disease, creates substantial risks for CRC development. Mucosal damage from gut microbiota becomes worse because pro-inflammatory cytokines such as IL-6, IL-8, IL-17, and TNF-α are released into the system [137]. The inflammatory molecules trigger the activation of critical CRC progression pathways, NF-κB and STAT3. The colonic infection from E. faecalis causes mucosal inflammation while simultaneously damaging DNA and activating Smad4 signaling with cyclooxygenase-2 (COX-2) pathway function [138]. The inflammatory response enabled by Helicobacter pylori results in CRC development together with other pathogens. When NF-κB pathways become active along with Wnt pathways, it leads to an inflammatory cancer microenvironment that aids tumor formation [139].

Epigenetic Modifications and Cancer Progression

The progression of CRC depends heavily on three major epigenetic processes, which include DNA methylation together with histone modifications and non-coding RNA interactions [140]. The epigenetic mechanisms of gut bacteria control how genes express their information [141]. The immune system responds to short-chain fatty acids such as butyrate, which are derived from microbiota through histone modification to generate anti-inflammatory effects. The anti-inflammatory mechanism of butyrate occurs through histone methylation, which blocks NF-κB expression. Fecal microbiota transplantation (FMT) modifies DNA methylation patterns in CRC cells, which subsequently changes their tumor-related gene activity [142, 143]. FMT is investigated for use in CRC intervention because of its ability to restore the microbial balance. Although promising, there are major reservations about its safety, patient heterogeneity, and long-term outcomes that together pose barriers to its acceptance as a viable treatment. Safety remains a concern because FMT is associated with risks of pathogen infection, immune reactions, and microbiome alteration [144]. Even the most stringent donor selections can fail to identify some infections and drug-resistant organisms, which could be devastating to CRC patients with compromised immune systems. Besides, the alteration of the microbiota can cause inflammatory or metabolic activities, which might be detrimental to the patients. The effectiveness of FMT is further compromised by patient differences. With variations in the constituents of the gut microbiome, genetic factors, and immune responses, not all patients will benefit from the pro-

cedure [145]. Moreover, some microbiome donors are not useful because the microbiome of some people is less effective than others in modifying the state of the gut. But, until there are more individualized approaches, the results will remain erratic and uncertain. The long-term impacts of the use of FMT for CRC are still unknown. While improvement in gut microbiota after FMT is noted, the sustainability of these changes is frequently—and problematically—short-lived, necessitating repeat procedures. There is also concern that FMT might unintentionally transfer pathogenic bacteria that might exacerbate cancer instead of control it. Furthermore, unpredicted changes in metabolic and neurological activity point towards the need for further investigation. Standardized protocols, improvement in donor selection criteria, and alternative microbiome-based approaches such as next-generation probiotics are needed to assess FMT's safety and effectiveness. Until understanding of greater long-term consequences is reached, FMT is best restricted to clinical trials rather than CRC management outside the clinical setting.

Microbial Dysbiosis in CRC: Cause or Consequence

Newer lines of research suggest that specific bacteria may be important players in the etiology of CRC [146]. For instance, *Fusobacterium nucleatum* is often detected in CRC tumors, and has been shown to undermine immune response, trigger several tumorigenic processes such as Wnt pathway signaling, and further aid in chemoresistance [71]. Likewise, toxin-producing *Bacteroides fragilis* is known to perpetuate CRC through chronic inflammation and epithelial ulceration, while polyketide synthase positive (pks+) *Escherichia coli* strains synthesize a genotoxic compound known as colibactin, which damages DNA and causes mutations that may initiate tumors [147]. Data from cohort studies and germ-free mice studies indicate that these bacteria are not simply passive colonizers but may actually participate in the causation of CRC.

On the other hand, CRC is also causing a disease that may transform the conditions in which plunging shifts in microbial populations occur, instead of microbiota being the primary driver of the disease. Changes in tumor metabolism, including changes in mucus hypersecretion, hypoxic conditions, as well as immune enhancement and some other processes, may create an environment that is favorable to the growth of certain bacterial species and unfavorable to others [148]. Besides, the inflammation and tissue remodeling that come with the progression of CRC may influence what microbes are able to colonize particular tissues. Also, changes in diet, use of antibiotics, and exposure to chemotherapy in CRC patients are likely to greatly alter the gut microbiome and disprove whether it is dysbiotic before or after the tumor.

Untangling this bidirectional relationship remains a challenge, and additional probing is required to ascertain if microbial dysbiosis stems from or leads to CRC. The development of causal relationships will be possible with longitudinal cohort studies and the analysis of functional microbiomes combined with interventional studies. All of these steps would enhance the understanding of the role of the microbiome in CRC and underscore its value as a biomarker or therapeutic target.

Hypothesis Models Associated With Intestinal Microbiota and Colorectal Cancer (CRC)

CRC occurrence is linked to alterations in the intestinal microbiota structure as well as infections with specific bacteria. To better understand this relationship, researchers have proposed several hypotheses:

The Alpha-Bug Hypothesis: Based on their ApcMin/+ mouse studies, Sears and Pardoll established the "Alpha-bug" hypothesis. The rapid activation of signal transducer and activator of transcription-3 (STAT3) occurs within ETBF exposure when accompanied by T helper 17 (Th17) responses that lead to colitis, which might promote cancer development with modified colonic epithelium [149].

The hypothesis unites research on both individual intestinal bacteria and microbial community dynamics to study carcinogenic mechanisms. Alpha-bugs cause tumors directly and simultaneously reshape bacterial communities to increase tumor-forming potential. The presence of Alpha-bugs leads to the suppression of bacteria that protect against cancer in the intestinal tract. The potential Alpha-bug agents consist of ETBF alongside Streptococcus bovis and superoxide-producing *Enterococcus faecalis* alongside *Escherichia coli* [149].

The Driver-Passenger Model: Next-generation sequencing technology enables researchers to detect bacterial species that are linked to CRC development. According to Tjalsma *et al*. [150], bacterial microbes fall into two distinct groups based on their role in the human body.

(a) The initiation of CRC begins when driver bacteria found in the human gut produce toxic substances that damage cell DNA in the epithelium.

(b) The tumor environment allows the growth of opportunistic bacteria which including Fusobacterium spp., to contribute to tumor progression [86,150].

The driver-passenger model for CRC contrasts with Alpha-bug by describing how driver bacteria begin tumors but passenger bacteria replace them during tumor progression.

Influence of the Gut Microbiome on CRC Treatment

Medical experts have established a direct relationship between gut microbiome and colorectal cancer (Fig. 3), which leads to extensive research about its impact on CRC

Table 4. Overview of bacterial influence in colorectal cancer.

Phyla	Genus/Species	Mechanism	References
Harmful Bacteria			
Fusobacteria	*Fusobacterium nucleatum*	Increased abundance; FadA binding to E-cadherin, activation of β-catenin signaling, NF-κB activation, production of IL-6, IL-8, Myc, cyclin D1 activation	[172]
Bacteroidetes	*Bacteroides fragilis*	Increased abundance; BFT toxin, activation of STAT3, Th-17 immune response induction, production of IL-1, activation of β-catenin signaling	[67]
Firmicutes	*Clostridium spp.*	Increased abundance; ROS production, DNA damage, production of Deoxycholic Acid (DCA)	[173]
Proteobacteria	*Escherichia coli*	Increased abundance; Colibactin production, DNA damage	[174]
Actinobacteria	*Slackia*	Increased abundance; Anti-oxidant potential	[175]
Bacteroidetes	*Bacteroides vulgatus*	Increased abundance; NF-κB activation	[176]
Firmicutes	*Streptococcus bovis*	Increased abundance; Expression of cyclooxygenase-2 (COX-2)	[177]
Actinobacteria	*Atopobium parvulum*	Increased abundance; Central hub of H_2S producers	[178]
Firmicutes	*Enterococcus faecalis*	Increased abundance; ROS production, DNA damage	[179]
Bacteroidetes	*Prevotella spp.*	Increased abundance; Inflammatory response	[180]
Firmicutes	*Parvimonas*	Increased abundance; Inflammatory, immune response	[181]
Firmicutes	*Peptostreptococcus*	Increased abundance; Oxidative stress	[182]
Proteobacteria	*Helicobacter*	Increased abundance; Inflammatory response	[183]
Beneficial Bacteria			
Firmicutes	*Roseburia spp.*	Decreased abundance; Anti-inflammatory, butyrate production	[184]
Actinobacteria	*Bifidobacterium spp.*	Decreased abundance; Immune modulatory, anti-inflammatory, butyrate production	[185]
Firmicutes	*Lactobacillus spp.*	Decreased abundance; Immune modulation (T-cell activation), mucus barrier maintenance	[186]
Proteobacteria	*Salmonella spp.*	Decreased abundance; Reduction of Shiga and Shiga-like toxins	[187]
Proteobacteria	*Shigella spp.*	Decreased abundance; Reduction of Shiga and Shiga-like toxins	[188]

treatment. Research on tumor therapy focuses on the microbiome as a crucial field of cancer investigation that evaluates its joint usage with different treatment approaches for potential clinical benefits [11,151].

In addition to traditional chemotherapy and radiotherapy, emerging findings highlight the synergistic effects of the gut microbiome with immune checkpoint inhibitors (ICIs) [152].

Chemotherapy

Conventional chemotherapy treatment effectiveness depends on the state of gut microbiota. The anti-cancer drug metabolism performed by specific microbial species results in altered toxicities of these drugs [153]. The administration of antibiotics to mice results in lower anti-tumor chemotherapy responses to platinum-based drugs, including oxaliplatin and CpG oligodeoxynucleotides. Cytokine secretion and reactive oxygen species (ROS) production diminished as a result of which tumor necrosis decreased [154]. The therapeutic value of gemcitabine decreases when gammaproteobacteria found in tumors activate a specific enzyme, which makes the drug inactive. Bacteria that contain an extended cytidine deaminase enzyme form carry out the conversion of gemcitabine into an inactive metabolite. The removal of bacteria by antibiotics made gemcitabine effective again when used to treat CRC mice [155].

The administration of antibiotics led to decreased anti-cancer effects of 5-fluorouracil (5-FU) in tested studies [156]. Antibiotic-induced pathogenic bacteria growth of *E. coli* or *Shigella spp.* and Enterobacter was found through microbiome analysis (Fig. 3), but probiotic supplements restored the microbiome to its original state [157]. *Fusobacterium nucleatum,* which advances CRC, has been shown to decrease chemotherapy response effectiveness in patients (Fig. 3). High concentrations of *F. nucleatum* lead to chemotherapy resistance through its effects on apoptosis and immune pathway activation as well as its promotion of chemoresistance mechanisms [158].

Radiotherapy

The dysbiosis caused by radiotherapy treatment negatively affects treatment results for patients with CRC. Beneficial gut bacteria Bifidobacterium, Faecalibacterium, and Clostridium decrease post-radiation (Fig. 3), while Bacteroides and Enterococcus species numbers increase [159]. The population of Fusobacteria in pelvic radiation therapy patients showed an increase of about 3%, which might contribute to tumor progression. Gut barrier impairment caused by radiation creates an entry point for these bacteria to penetrate tissues, leading to more severe inflammation and increased tissue damage [160].

Immunotherapy

A well-functioning gut microbiome regulates both immune system responses while influencing the effectiveness of immunotherapeutic treatments. Scientific evidence shows that gut bacteria, which live in harmony with the human body, boost the cancer-fighting capabilities of PD-L1 inhibitors. The most commonly used immunocheckpoint inhibitor, Cytotoxic T-Lymphocyte Antigen 4 (CTLA-4), exhibits treatment effectiveness that depends on the composition of patients' microbiome. Research has shown that the Bacteroides species act as principal mediators that influence CTLA-4 blockade activity [161–163].

The effectiveness of PD-L1 inhibitors depends on how different bacterial types make up the gut microbiota. Research indicates that anti-tumor effects occur when gut bacteria contain Akkermansia, Faecalibacterium, Clostridiales, and Bifidobacterium species [164]. Microbiome bacteria benefit immune responses through their ability to produce SCFAs and specifically butyrate and propionate. Akkermansia muciniphila demonstrates its ability to enhance immunotherapy effects by establishing IL-12-dependent cell interactions with dendritic cells found in lymph nodes. The immune response against tumors gets better when Bacteroides species activate both Th1 cells and CD8 T cells [165–169].

Microbiota as Biomarkers for CRC Diagnosis

The changes in gut microbiota function as a promising tool for cancer diagnosis and the prediction of CRC development. Research into faecal samples through metagenomic analyses has unveiled three specific bacterial species linked to CRC formation, namely *Fusobacterium nucleatum*, *Porphyromonas*, and *Parvimonas* [25,168–171] (Table 4, Ref. [67,172–188]). *F. nucleatum* levels that rise in CRC patients indicate potential diagnostic value for this bacterium. The existence of choline trimethylamine lyase (cutC) together with other microbial enzyme genes has been identified as an indicator for CRC development. Microbiologic analysis of stool samples reveals fundamental data for detecting CRC early [47,169–171].

Role of Diet in CRC Prevention

The way people eat food creates substantial changes in their risk of developing CRC. Eating excessive amounts of animal proteins and fats stimulates secondary bile acid together with hydrogen sulfide formation, which damages gut barriers and results in inflammation and DNA damage [189]. The consumption of dietary fiber triggers the production of SCFA that acts as an anti-inflammatory agent and shows anti-cancer properties [190,191]. Research shows that consuming a diet full of fiber and fruits and vegetables helps decrease CRC risk, yet consuming large amounts of red meat combined with alcohol usage increases this risk.

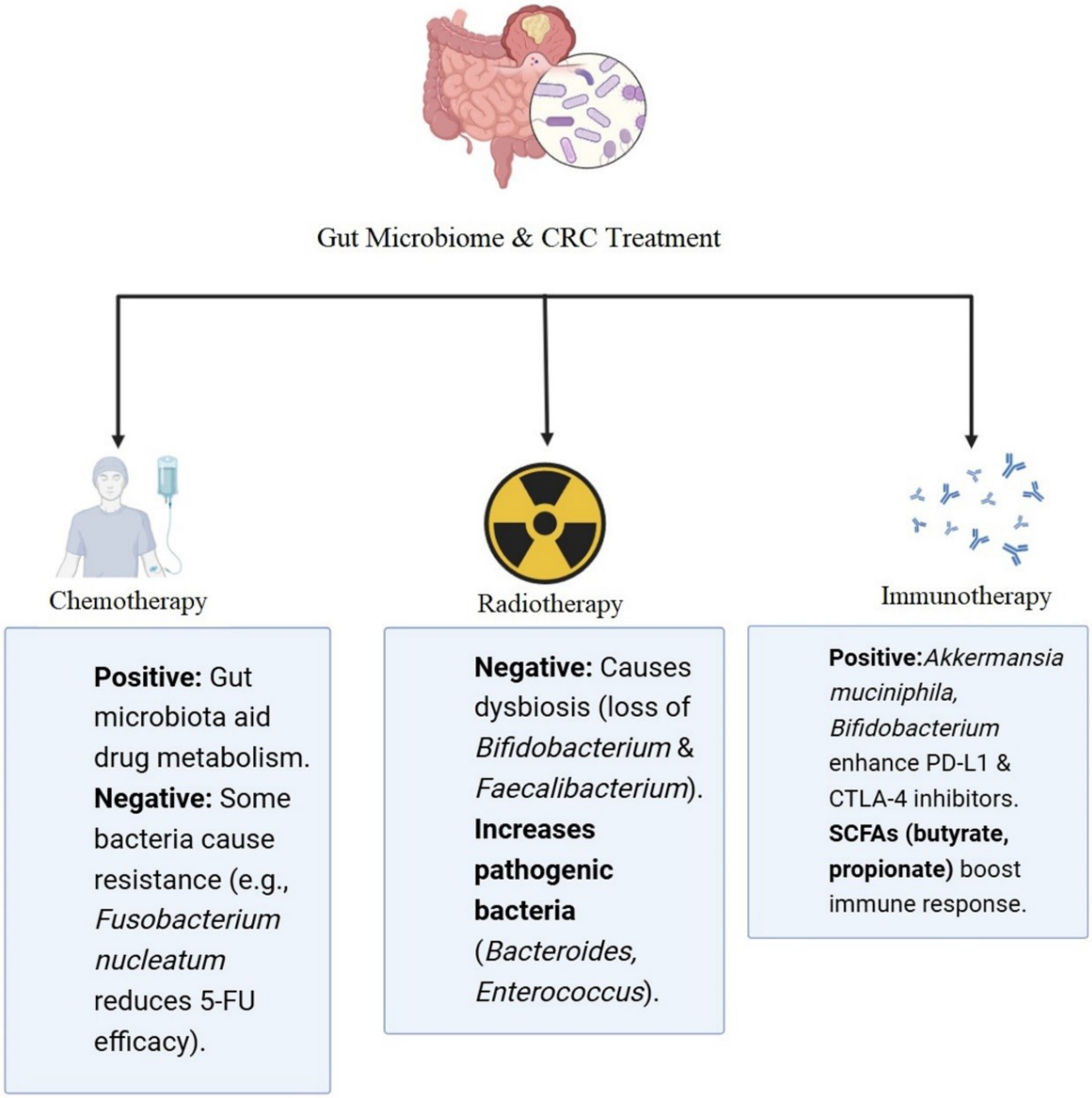

Fig. 3. The Influence of the Gut Microbiome on CRC Treatment. The gut microbiota plays a crucial role in chemotherapy, radiotherapy, and immunotherapy responses. Certain bacteria (e.g., Akkermansia muciniphila, Bifidobacterium) enhance immune checkpoint inhibitors, while others (e.g., *Fusobacterium nucleatum*) contribute to chemotherapy resistance. Radiotherapy-induced dysbiosis can worsen treatment outcomes by disrupting beneficial bacterial populations. Understanding these interactions can help improve CRC treatment strategies. Biorender software (https://www.biorender.com/) was used to create the figure. 5-FU, 5-fluorouracil; PD-L1, Programmed Death-Ligand 1; CTLA-4, Cytotoxic T-Lymphocyte Antigen 4; SCFAs, short-chain fatty acids.

Plant-based foods containing flavonoids demonstrate protective properties that slow down CRC development [192].

Faecal Microbiota Transplantation (FMT) as a Therapeutic Approach

Medical research indicates that FMT demonstrates potential as a treatment for IBD and CRC because it helps maintain proper gut microbiota equilibrium. Anti-PD-1 immunotherapy receives a boost from FMT through its ability to strengthen T cell responses against tumors, according to research findings [193]. The positive immunotherapy response of patients correlates with higher numbers of beneficial gut microorganisms, Bifidobacterium and *Enterococcus faecalis,* along with other diverse species [194].

Use of Probiotics, Prebiotics, Synbiotics, and Postbiotics in CRC Prevention

The beneficial microorganisms Lactobacillus and Bifidobacterium improve gut health together with immune function. Research indicates L. acidophilus and L. plantarum show potential to stop CRC development in people who have polyps or a CRC family history [195].

Prebiotics represent dietary compounds that stimulate the development of beneficial bacteria in the body. Gut health receives benefits from fructans, inulin, and galactooligosaccharides (GOS), which reduce CRC risk through their ability to control gut microbiota [196]. When probiotics and prebiotics work together in synbiotics, they create enhanced benefits for both types of bacteria [197]. CRC risk reduction occurs through immune response modulation by combining oligofructose-enriched inulin with L. rhamnosus and B. lactis probiotic strains [198]. Intestinal health support comes from bioactive compounds that gut bacteria generate through their production of postbiotics [199]. The protective postbiotic compound P40 that emerges from L. rhamnosus GG shows anti-inflammatory properties, which reduce CRC development potential [200].

Future Perspectives and Research Directions

Medical research in colorectal cancer moves ahead quickly through focused development of gut microbiome research and new therapeutic methods and early diagnosis approaches, and personalized treatments. The most potentially successful approach involves using microbiome-based diagnosis as part of regular screening programs [201]. The development of metagenomics and transcriptomics, and metabolomics research provides scientists with better comprehension of microbial signatures related to CRC development risks and disease progression [202]. Artificial intelligence (AI) together with machine learning can be utilized to study gut microbiota patterns for the detection of at-risk patients who will develop malignancies. Early-stage CRC detection through these technologies would provide an effective supplement to colonoscopy and fecal occult blood tests by improving access while maintaining low expense and non-invasive nature [203]. Scientists today use improved knowledge about how gut microbiota interacts with the immune system to develop targeted immunotherapy treatments. Immunotherapy response using immune checkpoint blockers gets enhanced when the bacterial strains of gut microbiota regulate immune responses effectively. Future studies will investigate methods to adjust the microbiome through dietary changes and prebiotics and probiotics, and FMT to enhance the success rates of immunotherapy [204]. Bacteriophages serve as select pathogens that destroy harmful bacteria, which provides an intriguing opportunity to modify the microbiome. By targeting cancer-associated bacteria with phage therapy, medical professionals could achieve precise bacterial elimination while preserving helpful microorganisms and restoring gut homeostasis, but reduce inflammatory responses [205]. Research now focuses on making microbial metabolites into therapeutic drugs for medical use. Potent anti-inflammatory together with tumor-suppressive properties distinguish the short-chain fatty acids such as butyrate and propionate [206]. The therapeutic potential of metabolites can be developed by controlling bacteriological strains through dietary approaches or engineered probiotic strains, which present a promising and low-risk method for cancer prevention along with management. Personalized nutrition developed from analyzing someone's microbiome profile has become a prominent preventive strategy [207].

Through microbiota analysis in patients, doctors can develop personalized nutrition strategies to improve health-promoting bacteria while decreasing potential CRC factors. Medical research has begun investigating the way lifestyle behaviors involving workouts and stress reduction techniques affect the microbial content in human intestines. Research indicates that physical exercise boosts bacterial diversity while supporting anti-inflammatory bacteria, although chronic stress creates dysbiosis and makes individuals more prone to CRC [114]. Knowledge about these relationships enables the creation of complete lifestyle programs that prevent CRC. New pathways for CRC treatment emerge from the pharmaceutical research that combines microbiota studies. Drug metabolism depends on the gut microbiome, which controls both chemotherapy agents' effectiveness and their harmful side effects. Current research investigates how to develop microbial biomarkers for predicting chemotherapy and immunotherapy responses, which will result in better treatment methods. Postbiotics show potential as CRC adjunct therapies because they demonstrate the ability to control inflammation and tumor growth according to research. Researchers are presently investigating the effects of the gut-brain axis on CRC development processes [208].

The connection between psychological conditions, including chronic stress and anxiety, and depression leads to gut dysbiosis that possibly affects CRC development through neuroimmune pathways. Psychological interventions and their effects on gut microbiota and CRC outcomes, including mindfulness-based stress reduction and cognitive-behavioral therapy, need further investigation to develop new preventive and therapeutic measures [209]. Future medical trials need to prove emerging strategies by conducting extensive assessments at multiple research facilities. The current promising findings need to undergo extensive research before they can be effectively translated into safe and reproducible clinical treatments. The regulatory systems must evolve to accept microbiome-directed interventions since they present essential differences from standard cancer therapy approaches. Researchers need to address ethical aspects related to FMT procedures alongside the modifications of microbiota genetics and privacy concerns regarding patient microbiome data collection in research. The combination of microbiome science together with precision oncology establishes a new standard in the treatment of CRC. Future cancer therapies will embrace a system-wide approach that consists of studying the entire host-microbe ecosystem because the microbiome functions as a critical factor in cancer pathophysiological pro-

cesses. Researchers from microbiology and oncology and immunology, and computational biology fields must work together to translate these findings into practical healthcare solutions. The purpose of advancing research is to create a complete framework that integrates microbiome knowledge for preventing cancer and detecting it early, and delivering individualized treatments to enhance patient survival rates and minimize the worldwide impact of this disease.

Research Gaps, Opportunities, and Ethical Issues

Although strides have been made toward understanding the association between gut microbiota and CRC, considerable gaps in research still exist, which pose barriers towards the integration of microbiome-based approaches into clinical practice. One prominent gap is the absence of longitudinal studies, which could firmly establish specific microbial changes and CRC development. Cross-sectional studies have been done, which point to some microbial signatures related to CRC, but it is still not clear whether these changes lead to tumorigenesis or if they are the byproducts of the disease. Longitudinal cohort studies that monitor changes in microbiome constituents before CRC diagnosis would be beneficial in resolving this issue.

The standardization of microbiome analysis methods is another difficulty. Differences in sequencing techniques, as well as bioinformatics pipelines and sample collection methods, lead to discrepancies in the scope of microbiome studies, which hinders inter-study comparisons. The establishment of universally accepted procedures for microbiome profiling will be vital in translating research results into clinical practice.

Even though probiotics, prebiotics, diet changes, FMT, and bacteriophage therapy boast potential as probiotics microbiome interventions, the claim is yet to be substantiated from human trials. Further testing through rigorous randomized control trials (RCTs) is necessary to establish if these interventions are the most effective in delivering the desired results long-term. Additionally, the gap concerning FMT and microbiome engineering for ethical and regulatory issues in ensuring safety for patients while complying with changing medical standards needs further examination.

The use of antimicrobial derivatives for the intended use of prevention and treatment of CRC is another case that lacks insight. Some short-chain fatty acids like butyrate and propionate have anti-inflammatory and tumor-suppressive effects; however, how they influence the progression of CRC is still unclear and requires additional research. New treatment methods can be adopted by identifying important strains that produce beneficial microbial metabolites and enhancing their effect by diet or use of probiotics.

While the gut-brain axis is known to affect the progression of CRC, the influence of psychological components, including stress, anxiety, and depression, on the gut microbiome and CRC remains understudied. Illnesses could be helped by understanding how the neuroimmune system influences these interconnections, allowing the creation of broad treatment approaches that combine psychology with other forms of therapy.

Yet, the combination of AI and machine learning in research on the microbiome holds great promise for the prediction and detection of CRC risks. Unfortunately, models need to be constructed, tested, and validated for accuracy within different populations. Also, ethical issues pertaining to data privacy in relation to microbiome-based diagnostics must be managed for wider acceptance of such tests.

Closing these research deficits will require synergetic efforts from microbiologists, oncologists, immunologists, computational biologists, and bioethicists. With more research directed towards the role of the microbiome in CRC, there is likely to be a decrease in the incidence of CRC through better screening, prevention, and treatment strategies.

One of the major risks is the lack of predictability associated with microbiome interventions, especially in immunocompromised CRC patients. Changing gut microbiota through FMT or probiotics can have serious consequences, such as introducing a pathogen into the patient or dysregulating the immune system in an undesirable manner. The long-term effects of these therapies are unknown and set the stage for the need for clinical trials to determine safety and efficacy. Further, many patients with the same condition and diagnosis are likely to have very different gut microbiome compositions, and this phenomenon will likely result in variable outcomes from treatment, further highlighting the need for personalized solutions to healthcare.

Another set of ethical issues regarding microbiome therapies stems from the FMT rationale and protocol. The matter of donor selection, informed consent, as well as possible exploitation and commercialization of microbiota-based treatment poses large risks that need to be monitored for the protection of patients. In addition, modifying gut bacteria genetically for treatment purposes presents ethical concerns with lifestyle changes that may need to occur and regulatory questions that lack answers.

Lack of uniformity is still a significant hurdle for the implementation of microbiome therapies in conventional CRC treatment. Differences in microbiome intervention sequencing, sample collection, and even dosing interventions result in low reproducibility in studies. In any therapeutic approach, defining distinct boundaries for the application and analysis of the microbiome could guarantee uniformity and clinical validity.

Conclusion

Understanding the function of the gut microbiota in colorectal cancer is needed for creative ways to prevent

and treat it. Studies show that particular types of bacteria play a part in CRC development by creating inflammation and producing genotoxic effects while modifying immune responses. New breakthroughs in microbiome sequencing and metagenomic analysis revealed possible microbial biomarkers to aid in CRC screening and early detection. In addition, the interventions of gut microbiota, including diet modification, probiotics, prebiotics, and fecal microbiota transplant, are potentially effective in preventing CRC and improving treatment of CRC. Researchers need to conduct additional investigations to understand exactly how gut microbiota affect CRC development and to improve microbiome-based treatments for clinical use.

Availability of Data and Materials

Not applicable.

Author Contributions

Conceptualization, RM. Data Curation, RM, SA, WA and GA. Formal Analysis, SSA, RIA, HSA, MFA, AA, ORA, and RA. Investigation, RM, SA, WA, GA and SSA. Visualization, RM, SA, WA and GA. All authors were involved in the drafting and critical revision of the manuscript. All authors have read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

The authors acknowledge the funding obtained from the Research, Development, and Innovation Authority (RDIA), Saudi Arabia, Riyadh, Reactivating & Rebuilding of Existing Labs Initiative, number (13262-Tabuk-2023-UT-R-3-1-HW), supporting the generation of these data and publication.

Conflict of Interest

The authors declare no conflict of interest.

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