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# Regulation of Gut Microbiota: Is It Hope for Cure of Colorectal Cancer?

## Bağırsak Mikrobiyotasının Düzenlenmesi: Kolorektal Kanser Tedavisi İçin Umut mu?

Sadettin ER[1] [ID], Aylin KAHYAOĞLU[2] [ID], Bülent Cavit YÜKSEL[1] [ID], Sabri ÖZDEN[3] [ID], Kemalettin YILMAZ[4] [ID], Tezcan AKIN[1] [ID], Erdinç ÇETİNKAYA[1] [ID], Hüseyin BERKEM[1][ID], Mesut TEZ[1] [ID]

[1]Department of General Surgery, Ankara City Hospital (Bilkent), Ankara, Türkiye.
[2]Department of Medical Microbiology, Gulhane Training and Research Hospital, Ankara, Türkiye.
[3]Department of General Surgery, Konya City Hospital, Konya, Türkiye.
[4]Department of Gastroenterology, Lokman Hekim Etlik Hospital, Ankara, Türkiye.

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Correspondence: Sadettin Er; Assoc. Prof., Department of General Surgery, Ankara City Hospital (Bilkent), Ankara, Türkiye.
E-mail: ersadettin74@gmail.com

**Abstract**

The gut microbiota dysbiosis is linked with inflammatory bowel diseases, hypertension, atherosclerosis, hepatitis, neuropsychiatric disorders, diabetes, obesity, asthma, and development of cancer. Despite the substantial developments in oncology, cancer is still not in the category of curative diseases. However, significant steps are being taken in this direction through the identification of factors that play a role in the stages of complex carcinogenesis. Recent data obtained from human gut microbiota has shown that commensal microorganism species living on the epithelial surfaces of the intestines have an active role in this process and are also associated with personal responses to cancer treatment and toxicity. We now know more about the role of *Fusobacterium nucleatum*, an important member of the gut microbiota complex, as well as other microorganisms in the formation, treatment, diagnosis, and screening of colorectal cancer. In conclusion, the growing knowledge of microbiota, a key factor in colorectal cancer formation and treatment stages, will be able to change the early detection, treatment, and follow-up of these cancers. In this review, the role of gut microbiota in colorectal carcinogenesis and cancer formation mechanisms, significance in treatment and prognosis, and potential use in cancer prevention and screening have evaluated based on the data obtained from recent studies.

Keywords: Colorectal cancer, Carcinogenesis, Microbiota, *Fusobacterium nucleatum*.

**Özet**

Bağırsak mikrobiyota disbiyozu inflamatuar bağırsak hastalıkları, nöropsikiyatrik bozukluklar, hipertansiyon, ateroskleroz, hepatit, diyabet, obezite, astım ve kanser gelişimi ile ilişkilendirilmektedir. Onkolojideki önemli gelişmelere rağmen kanser halen tamamen tedavi edilebilir hastalıklar kategorisinde yer almamaktadır. Ancak kompleks karsinogenezin evrelerinde rol oynayan faktörlerin belirlenmesi ile bu yönde önemli adımlar atılmaktadır. İnsan bağırsak mikrobiyotasından elde edilen son veriler, bağırsakların epitelyal yüzeylerinde yaşayan kommensal mikroorganizma türlerinin bu süreçte aktif rol oynadığını ve ayrıca kanser tedavisine ve toksisiteye verilen bireysel yanıtlarla ilişkili olduğunu göstermiştir. Bağırsak mikrobiyota kompleksinin önemli bir üyesi olan *Fusobacterium nucleatum*'un ve bazı diğer mikroorganizmaların kolorektal kanserin oluşumu, tedavisi, teşhisi ve taranmasındaki rolü hakkında günümüzde daha fazla şey biliyoruz. Sonuç olarak, kolorektal kanser oluşumunda ve tedavi aşamalarında önemli bir faktör olan mikrobiyota konusunda artan bilgi birikimi, bu kanserlerin erken teşhis, tedavi ve takibini değiştirecektir. Bu derlemede,

son çalışmalardan elde edilen veriler temelinde, bağırsak mikrobiyotasının kolorektal karsinogenez ve kanser oluşum mekanizmalarındaki rolü, tedavi ve prognozdaki önemi ve kanser önleme ve taramasında kullanım potansiyeli değerlendirilmiştir.

Anahtar Kelimeler: Kolorektal kanser, Karsinogenez, Mikrobiyota, *Fusobacterium nucleatum*.

## Introduction

The colon and rectum are full of microorganisms with distinct complex groups that play a critical role in continuing homeostasis [1]. Therewithal, nowadays according to different studies, attention is being paid to microbiota causing the development of colorectal cancer (CRC) and to the death of patients [1].

Microbiota describes all species living with humans in a defined environment, while microbiome is a common expression used for the collection of genomes from all the organisms including viruses, bacteria, archaea, fungi, and etc. living on the surfaces of epithelial barriers and also other microbial structural elements [2–4]. These microorganisms have an effect on many physiological functions, especially hematopoiesis, inflammation, and immunity [5]. Furthermore, in related studies, the terms 'eubiosis' and 'dysbiosis' are being used to refer to healthy and unhealthy microbiota, respectively [6]. In general terms, gut microbiota act as a metabolic organ fulfilling many of the essential functions required for the protection of human health [7].

Alterations in the gut microbiota may cause the growth of microorganisms that act as warning of genomic mutations or aggravating a tumor [3,8]. The development of CRC is connected to many important predisposing factors, including advanced age, family history, male gender, sexual activity, colon polyps, genetic mutations, environmental factors, and a variety of dietary effects [9]. Toxic habits, such as tobacco and alcohol consumption are also linked to an increase in the risk for CRC [9]. There is a large amount of evidence that the complex gut microbiota community plays an important role in the development of CRC [3,10]. Gut microbiota, located in the gastrointestinal tract, has been found to be related to the development of CRC based toxic and genotoxic metabolites production from the fermentation of dietary ingredients [3,11].

The initiation, progression, and development of tumors are connected to the modifications of the activities of intestinal microorganisms. Nowadays, for specific microbes and microbiotas, unraveling host-microbiota interactions with environmental factors in carcinogenesis, as well as for cancer diagnosis and treatment has become a focus of intense interest [12,13]. Microbiota alterations have been especially reported in gastric cancer and CRC [14]. The normal gut microbiota provides a natural protection from diseases in the gastrointestinal system by inactivating microbial enzymes resulting in anticarcinogenic effects. These symbiotic interactions between resident microorganisms and the alimentary tract have an extremely important contribution to the protection of gut homeostasis. Alterations in the structure of microbiome can disrupt this symbiotic relationship and cause diseases, such as CRC [8]. Bacteria metabolize meat proteins and produce nitrosamines, which cause the formation of colon tumors that can be seen in animal models [15,16]. *Fusobacterium nucleatum*, *Escherichia coli*, *Enterococcus faecalis*, *Streptococcus gallolyticus*, *Streptococcus bovis*, *Helicobacter pylori*, and enterotoxigenic *Bacteroides fragilis* are nominee microorganisms that were demonstrated as initial triggers in the development of CRC [3,8,17]. However, none of these bacteria have been shown to have a relation with CRC [17], and none of the studies have shown that elimination of these organisms in human beings prevents CRC. For this reason, research on the change of intestinal microbiota especially in the presence of adenomatous polyps, which are precancerous lesions, are still actively carried out. It is well known that CRC generally develops due to serial mutations after adenomatous changes [18]. Patients with adenomatous polyps have been reported to have increased abundance of *Fusobacteria* when compared to the normal rectum mucosa of healthy subjects [3,19]. In the

studies, sessile serrated adenoma that causes right colon cancer and interval CRC is well known to develop CRC due to distinct from classic adenomatous polyps [20]. Recent studies have shown that some gut microbiota organisms, especially *F. nucleatum*, plays an important role in the development, progression, and invasion of CRC [21,22].

We aimed to assess the role of intestinal microbiota in colorectal carcinogenesis and cancer formation, treatment, prognosis, prevention, and screening based on the data obtained from the recent studies reviewed in this paper.

## Colorectal cancer

*Epidemiology*

Globally, CRC is the second most common cancer among women and third among men [23]. Nearly 75% of deaths occur in CRC patients over 65 years of age and mortality rates are higher in male patients [23,24]. Approximately 75% of CRC cases occur spontaneously while the remaining 25% have a family history of CRC, which demonstrates the contribution of genetic and environmental factors. However, genetic predisposition is low; only around 5-6% [25].

*Carcinogenesis*

Although many studies in the literature investigated the relationship between genetic and environmental risk factors and carcinogenesis, the molecular mechanisms of this interaction are very complex and are still not fully understood [26–28]. Some studies have implicated fiber deficiency in diet [28], while others considered red meat in diet and geographical differences to be major responsible factors [29–32]. In a meta-analysis, adiponectin levels were inversely associated with CRC risk [26], also leptin levels that are increased in obese patients were directly associated with CRC predisposition [33].

The changes in the gastrointestinal lumen and colonic epithelium are regulated by the genetic predisposition of individuals; furthermore, recently, microbiota has also emerged as an increasingly important factor. The gut contains components that affect the health of the colon, as well as the individual health, and interact with environmental factors and genetic characteristics of the person [34]. Due to its important role in human health, changes in gut microbiota have been associated with a variety of conditions, such as Crohn's disease, ulcerative colitis, enteric infections, diabetes, obesity, and especially CRC [3,35–37]. Studies have shown that gut microbiota affects cancer-related functions, such as cell proliferation, angiogenesis, and apoptosis [38,39], and that the initial composition of microbiota increases the risk of developing CRC in mice with impaired inflammatory function [40,41].

## Colon microbiota

The emergence of molecular techniques has allowed the identification of intestinal microorganisms that cannot be isolated and characterized by traditional culture methods [42,43], as well as the detection of nucleotide sequences of various microbial genes [44].

The large intestine is the main colonization site of the microbiota in the human body, and it is estimated that the gastrointestinal tract hosts around $10^{14}$ microbial cells [45,46]. Phylums of Firmicutes and Bacteroidetes are predominant strains in the large intestine, followed by phylums of Actinobacteria and Proteobacteria (Figure 1) [47]. Verrucomicrobia and Fusobacteria are also found in lesser amounts [47]. The colon has an oxygen-free reducing atmosphere, therefore most of the microbial populations in the colon are anaerobic and strains of *Bacteroides* are also abundant [48,49]. Recent studies have provided evidence that microbiota, particularly gut microbiota, is closely associated with initiation, progression, and dissemination of cancer both at epithelial barriers and in sterile tissues, thus may have a key role in carcinogenesis and can also change response to anti-cancer treatments and toxic side effect tendencies [50].

*F. nucleatum* is a gram-negative, anaerobic, opportunistic bacterial pathogen that has been most commonly associated with CRC [51]. In CRC patients, increased luminal colonization of *F. nucleatum* has been reported in colon adenomas and this bacterium has been isolated in higher number of copies in the CRC cases [52,53].

**Functions of microbiota**

Microbiota is involved in the transformation of gut vitamins, amino acid synthesis, ion absorption, dietary polyphenolic compounds, as well as the biotransformation of bile acids [54,55]. In connection with these metabolic functions, it also contributes to maintaining the function of the intestinal barrier for the development of the immune system and producing an adequate immune response against pathogens [56,57]. However, if these functions are impaired due to disruption of intestinal homeostasis (*dysbiosis*), this can lead to an overproduction of opportunistic pathogens inhibited by commensal bacteria [58]. Some of these increasing pathogenic bacteria are implicated in the development of CRC.

**Association between CRC and *F. nucleatum***

Changes in the composition, distribution, and metabolism of microbiota may alter homeostasis, thus initiating dysplasia and cancer in the colon [59]. Most studies available in the literature have investigated the association between CRC and *Fusobacterium* strains. For example, Mima et al. [60] found that the density of *F. nucleatum* gradually increased from the rectum to cecum, resulting in a high incidence of colon and ascending colon cancer. Castellarin et al. [10] confirmed that these microorganisms are found in excessive amounts in colorectal tumor tissues and invasive foci. Kostic et al. [21] also showed the presence of these species in human colonic adenomas. In another study, the prevalence of *F. nucleatum* in esophagus, stomach, and CRC tissues were reported to be 20%, 10%, and 45%, respectively [61]. In a recent report, it was revealed that chronic exposure of adenomatous polyposis coli $(APC)^{min/-}$ mice to invasive *F. nucleatum* increased the colonic tumor burden [21].

**Other gut bacteria responsible for CRC**

In patients with CRC, the composition of gut microbiota is associated with a persistent-opportunistic microbiome profile that can alter the existing mutual relationship between microbiota and host, resulting in a disease state [62,63]. CRC has also been associated with pathogenic strains other than *F. nucleatum,* such as *S. gallolyticus*, *H. pylori*, and *E. coli* [3,64]. Furthermore, an increase in *Porphyromonas*, *Peptostreptococcus*, and *Mogibacterium* has also been shown in the intestinal mucosa of patients with CRC [65]. A research by Burns et al. has also revealed that a tumor microbiome plays an active role in the development and/or progression of CRC in addition to revealing tumor microbial diversity [66].

**CRC formation mechanism of gut microbiota**

Several factors and mechanisms have been reported to contribute to the formation and progression of CRC; e.g., chronic inflammation of colon mucosa by inducing mutations, inhibiting apoptosis, and stimulating angiogenesis [67,68]; opportunistic pathogens by promoting the activation of mucosa permeability, bacterial translocation, and components of adaptive immune systems; and gut microbiota through chronic induction, genotoxin biosynthesis that interferes with cell cycle regulation, toxic metabolite production, and heterocyclic amine activation [3,63].

Although *B. fragilis* toxin is considered to be one of the main toxins in the development of CRC, other similar toxins have also been found in *E. coli, Salmonella enterica,* and *Shigella flexneri* [34]. This suggests that enterobacterial toxins are strongly involved in tumorigenesis [69]. Recent studies have shown that the tumor burden is based, in part, on the interactions between fusobacterial lectin Fap2 and host Gal-GalNAc, and that the binding of fusobacterial FadA adhesins to host cadherins can potentially stimulate the oncogenic beta-catenin signal, which may have a role in cancer formation [51,70,71]. It is important to bear in mind that *F. nucleatum* functions in a complex environment, and its effects are directly or indirectly influenced by other members of the microbial community, host factors in the tumor microenvironment, and tumor mutation profile. This reveals a clinical picture involving a multifactorial relationship between *F. nucleatum* and cancer [62]. It has also been suggested that secondary bile acids created by gut microbiota; i.e., deoxycholic acids and lithocholic acids, may act as a trigger for CRC by supporting apoptosis-resistant cells [72].

**Treatment**

Recent studies have shown that microbiota affects the response to chemotherapy and immunotherapy through myeloid cells in the tumor microenvironment [73]. A prebiotic is defined as a selectively fermented compound that allows specific changes in both host and components and/or activities with benefits for health in the gastrointestinal microflora [74]. Short-chain fatty acids (SCFAs), such as *acetate*, *propionate*, and *butyrate* and lactate prebiotics are produced by colonic bacterial fermentation of bioactive carbohydrates and not only play an important role in the prevention of CRC but also may have local and systemic biological effects [74,75]. It has also been reported that the colonic fermentation products of microbiota may have antimicrobial activity against bactericides that form CRC through the production of SCFAs and peptides [76]. SFCAs, especially butyrate, have been found to increase mucosal cell differentiation, support epithelial barrier function, modulate apoptosis, stop cell growth, detoxify electrophiles associated with oxidative stress, and modulate glutathione S-transferase and histone acetylation patterns [77,78].

In a recent study, in which gut microbiota manipulated using different combinations of antibiotic revealed that triple antibiotic regimen comprising vancomycin, streptomycin, and metronidazole completely block tumor formation [79]. *F. nucleatum* was found predominantly associated with cancer cells in the metastatic liver lesions, and metronidazole treatment of mice bearing colon cancer xenografts reduced the *Fusobacterium* burden, cancer cell proliferation, and overall tumor growth [80]. Thus, it was concluded that antimicrobial treatments may be useful as a potential treatment for *Fusobacterium*-associated CRC cases [80]. In another related study, intestinal tumorigenesis induced by *F. nucleatum* was inhibited by TAK-242 (*Toll-like receptor-4 antagonist*) treatment, which suggests that the Toll-like receptor-4 is a potential target for the prevention and treatment of *F. nucleatum* associated CRC cases [22].

In the International Probiotic Workshop held in Amsterdam in 2004, probiotics were defined as products (*bacterial and microbial therapeutic or bacterial immunomodulatory products*), whose health-related therapeutic effects have been proven in clinical trials [81]. Prebiotics, on the other hand, are defined as nutrients that pass directly into the large intestine without being digested in the small intestine and promote the growth and activity of probiotics in the intestinal tract; thus, they increase the beneficial effects of probiotics for health [82]. Compounds used as prebiotics include; lactulose, lactosucrose, inulin, fructo-oligosaccharides, galacto-oligosaccharides, soy-oligosaccharides, isomalto-oligosaccharides [82,83]. According to another known definition, prebiotics are carbohydrate molecules that stimulate the development of useful flora elements, such as *Bifidobacterium* and are not absorbed in the intestine [84]. Symbiotics is a term used for the combination of probiotics and prebiotics [84]. The International Scientific Association for Probiotics and Prebiotics discussed probiotics and described them as viable microorganisms that are beneficial for the host when applied in sufficient amounts [85]. Supportive benefits of probiotics to health can be summarized as antimicrobial activities against intestinal pathogens, modulation of the immune system, lowering of blood cholesterol levels, prevention of colitis, inflammation and colon cancer, and regulation of host energy metabolism [86]. In consensus statement on probiotics and prebiotics, it was once again stated that they regulate certain aspects of metabolic activity including colonocyte function, immune system, intestinal homeostasis, energy production, blood lipids, appetite, and kidney physiology [87]. In the literature, it has also been found that gut microbiota regulates therapeutic activities of anti-cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) and anti-programmed cell death protein 1. In mice without microorganisms or following antibiotherapy, the tumor response was found inadequate and colon mucosa injury induced by increased T cell response secondary to CTLA-4 antagonism was associated with changes in species, such as Clostridiales, *Bacteroides*, and *Burkholderia* present in gut microbiota [88].

Other studies investigating the benefits of probiotic treatments have shown that the

combination of probiotics, such as *Lactobacillus acidophilus* and *Bifidobacterium bifidum* can increase the antitumoral effect, as well as preventing some cisplatin-induced toxicities [89], the use of probiotics alone or in combination with nutritional supplements in cancer patients can improve cancer-associated cachexia [90], probiotics reduce gut injury induced by radiation, and TLR-2-activated microorganisms such as *Lactobacillus rhamnosus* in mice protect intestinal mucosa from the effect of radiotherapy through the transportation of cyclooxygenase-2 (COX-2) expressing cells from the villi to the base of intestinal crypts [91].

Probiotic therapy involving beneficial microorganisms to prevent postoperative harmful pathogens has emerged as a new therapeutic approach [92]. In a prospective study, patients underwent colorectal resection for benign reasons and using probiotic treatment following the end of postoperative antibiotic treatment were evaluated monthly and researchers reported that probiotic treatment decreased pain by the time and the cognitive state of the patients has significantly improved in the longer term [93]. In another study, *F. nucleatum* was reported to directly affect oxaliplatin and 5-fluorouracil chemoresistance in CRC via a TLR-4/MYD-88-dependent mechanism [94]. In the literature, it is also suggested that *F. nucleatum* is a novel biomarker for clinical management in patients with stage III/IV CRC, and targeting *F. nucleatum* may be an effective adjuvant approach to preventing metastasis and chemotherapy resistance in CRC [95].

**Prognostic significance of microbiota in CRC**

Bullman et al. [80] showed that among patients with cecum and ascending colon tumors, those with increased amounts of *Fusobacterium* have the lowest overall survival rate.

Oxaliplatin, an approved chemotherapeutic agent, induces immunological cancer cell death, stimulates anti-tumor immunoreactivity through antigen-presenting cells, and is able to provide long-term tumor regression and cure [96]. In mice that are deficient in microbiota, in addition to early genotoxic and cytotoxic effects, decreased long-term survival as a result of reduced adaptive immune response to oxaliplatin was reported [73].

Flanagan et al. [97] reported that *F. nucleatum* levels were significantly higher in patients with high-grade dysplasia, while CRC patients with lower *F. nucleatum* levels had a longer overall survival than those with moderate to high levels.

In another studies, it was found that *F. nucleatum* (subtype nucleatum ATCC 25586) increased in vitro and in vivo CRC cell proliferation, and exposure of $APC^{min/-}$ mice to *F. nucleatum* increased tumor burden and reduced survival rates [62]. Also, the increase in *F. nucleatum* and miR-21 levels in the tissues of patients with CRC and the presence of advanced disease were associated with poor prognosis [62]. Similarly, *F. nucleatum* was associated with aggressive course, poor outcomes, and post-treatment relapse in patients with CRC. It was also reported that *F. nucleatum* reformed tumor cells for survival after chemotherapy [94].

**Role of microbiota in preventing CRC**

According to previous literature, the use of probiotic bacteria, such as *Bifidobacterium* and *Lactobacillus* to prevent CRC has a role in reducing the CRC risk in humans [98]. Probiotics have been found effective in preventing known inflammatory responses, inhibiting colonization that causes known CRC, inactivating bacterial toxins, and reducing their production [99–102]. In another study, it was shown that the consumption of probiotics in both in vitro and animal models could prevent the development of CRC [103].

It has been shown that among SCFAs, butyrate is a source of energy for colonocytes and prevents the development of CRC, specifically through its protective activity for large intestinal functions, such as increasing as intestinal motility and visceral blood flow, preventing overgrowth of pathogens, reducing inflammation, inducing apoptosis, and inhibiting tumor cell progression [75,104–108]. It has also been found that dietary fibers cause SCFA production, thereby supporting colonic fermentation and inhibiting pathogen colonization, which reduces CRC risk [105,109].

**Role of microbiota in screening CRC**

The findings revealing the association of microbiota with cancer etiopathogenesis, treatment response and toxicity, and better understanding of the role of microbiota in carcinogenesis have brought about the hypothesis that it can be used in the diagnosis, treatment, and screening of cancer [52]. Studies conducted with patients having CRC have shown a significant difference in microbiota between cancerous and healthy tissues [110], and combining fecal occult blood tests with diagnostic metagenomic tests using *Fusobacterium* species increased the sensitivity of screening by 45% [111]. In a recent study, *F. nucleatum* were detected in CRC patients' stools in higher levels than in patients with dysplasia and controls with a sensitivity of 69.2% for CRC [112]. The sensitivity of screening tests in CRC, specifically that of fecal immunochemical test (FIT) and multitarget DNA test for detecting enlarged adenomas has been reported as 73.8% and 92.3% respectively [113]. Moreover, the combined use of FIT and fecal measurement of *Fusobacterium* can assess more than 75% of CRC samples that are not detected by FIT alone (92.3% vs 73.1%) [114]. This has led researchers to suggest that microbiota is a potential source of biomarkers, and many species have been proposed as biomarkers for CRC in the literature [115–118]. Such that in another study, *F. nucleatum* was shown to have a diagnostic and prognostic deterministic potential as a non-invasive biomarker in patients with CRC [97].

Regarding diagnosis and prognosis, there has been an attempt to use the fecal 16S rRNA gene sequence as a biomarker for CRC. As a result, it was emphasized that microbiome profile may be correlated with the T stage in CRC [119].

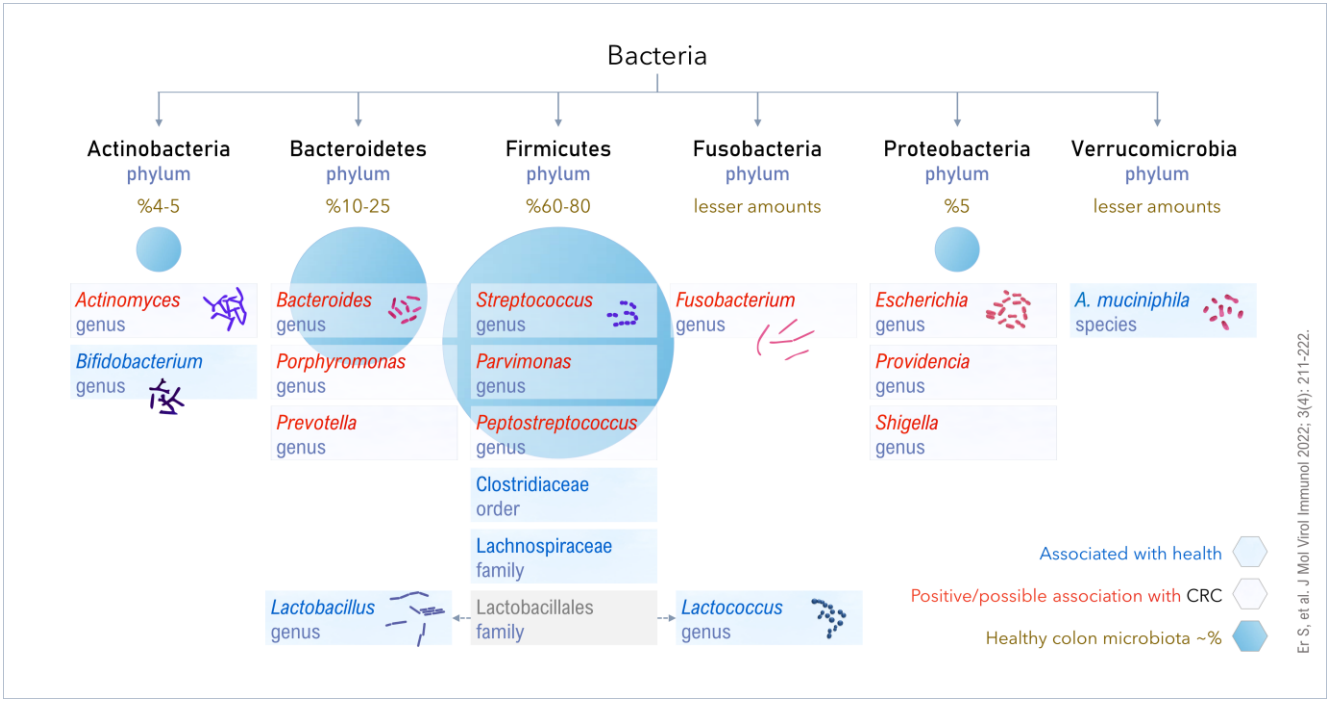


**Figure 1.** Overview of bacteria in the colon microbiota and their relationship with colorectal cancer [120]. The healthy colon microbiota is mainly composed of bacteria from the Firmicutes phylum. The second largest group consists of members of the Bacteroidetes phylum, while the Proteobacteria and Actinobacteria phyla are less frequent. Fusobacteria and Verrucomicrobia members are lesser amounts of the colon microbiota. Bacterial groups written in *red* in the figure are associated with colorectal cancer (*individually linked or increased abundance in faecal and tumor samples*), while written in *blue* are associated with the healthy condition.

**Next step in screening CRC**

Patients with colorectal adenomas have been characterized by the lack of potentially beneficial organisms, often from the Lachnospiraceae family (*androgenic species*) [121]. The findings of some related studies reveal that decreased butyrate-producing gut microbiota may lead to an increase in susceptibility to tumor formation [122]. With

this in mind, the best approach to microbiota-based screening may be to monitor patients' microbiota for an extended period of time to identify individual changes in its structure [123]. As with many other medical disciplines, microbiota-associated diseases may require a highly personalized approach for both screening and treatment in the future.

## Conclusion

The gut microbiota comprises many well-known microorganisms with complex functions in the human gastrointestinal tract and defined microbiota members may become important biomarkers in the future for screening, early diagnosis, guiding treatment, and predicting overall survival in CRC.

**Conflict of interest:** The authors declare that there is no conflict of interest. The authors alone are responsible for the content and writing of the paper. **Financial disclosure:** There is no financial support to this study.

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