# Composition and Diversity of Intestinal Microbiota in Colorectal Cancer and Potential Utilization in Diagnosis and Therapy

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## ABSTRACT

*Colorectal cancer is the third most common malignancy and the fourth most common malignancy causing death in the world. The development of colorectal cancer is influenced by several factors, including external, internal environmental, and genetic factors. One of the environmental factors recently known to be associated with colorectal cancer is gut microbiota. Generally, gut microbiota has various functions and is influenced by several factors, such as food, drugs, activities, habits, and diseases. Microbiota may become imbalanced, otherwise known as dysbiosis, which may lead to several changes and disturbances that can initiate the development of malignancy. There were differences in the composition and diversity of the types of microbiota in colorectal cancer patients. This difference has the potential to be used as a diagnostic marker and also the development of treatment in patients with colorectal cancer.*

***Keywords:*** *gut microbiota, colorectal cancer, diversity, abundance*

## ABSTRAK

*Kanker kolorektal merupakan keganasan ketiga yang paling sering ditemukan dan keganasan keempat yang paling sering menyebabkan kematian di dunia. Perkembangan kanker kolorektal dipengaruhi oleh beberapa faktor yaitu faktor lingkungan eksternal, internal serta faktor genetik. Salah satu faktor lingkungan yang baru-baru ini dikatakan mempunyai hubungan dengan kanker kolorektal adalah mikrobiota usus. Secara umum mikrobiota usus ini memiliki beragam fungsi dan dipengaruhi oleh beberapa hal seperti makanan, obat-obatan, aktifitas, kebiasaan dan penyakit. Mikrobiota dapat mengalami ketidakseimbangan yang disebut disbiosis yang dapat menyebabkan beberapa perubahan dan gangguan yang dapat menginisiasi timbulnya keganasan. Terdapat perbedaan komposisi dan kelimpahan jenis mikrobiota pada pasien kanker koloroektal. Perbedaan ini berpotensi digunakan sebagai marker diagnosis serta juga perkembangan tatalaksana pada pasien dengan kanker kolorektal.*

***Kata kunci:*** *Mikrobiota usus, kanker kolorektal, Keragaman, kelimpahan*

## INTRODUCTION

Colorectal cancer is a malignancy of the gastrointestinal tract involving the colon and rectum. This disease is the third most common malignancy and the fourth most common malignancy causing death in the world. [1] The mortality rate of colorectal cancer worldwide is 8.9 per 100,000 population. [2] This mortality rate varies according to the socioeconomic condition of a country.

The development of colorectal cancer is influenced by several factors, including internal and external environmental factors, and genetic factors. The genetical factor is predicted to play a role in 10 to 15% of overall colorectal cancer[3]. Genetic factor has a great role in colorectal cancer in patients younger than 50 years old. [4]. Due to that small percentage, other factors besides genetic factors, such as environmental factors, hold an important role in the pathogenesis and development of colorectal cancer. One of the environmental factors recently being widely studied is gut microbiota.

Gut microbiota consists of various types of microbes, including bacteria, viruses, fungi, and protozoa. [5]. Gut microbiota has a protective function and plays an important role in the metabolism process in the digestive tract. However, this gut microbiota may experience changes, known as dysbiosis. This may lead to metabolism disturbances in the intestines, immune system disturbances, chronic inflammation, and finally may trigger the emergence of a tumour cell or stimulate the progression of tumour cells. [6]

### Association of Gut Microbiota and Colorectal Cancer

Gut microbiota consists of a set of more than 100 trillion microbiota cells arranged in a complex manner, dominated by *Firmicutes, Bacteroidetes, Proteobacteria, and Actinobacteria filum*. [3,7] Generally this gut microbiota has various functions useful for the host, such as defense from pathogens, immune system modulation, and also as producing source of nutrients for the body's metabolism. [7]

Studies on microbiota in Indonesia are still limited. Studies performed by Rahayu ES et al in Yogyakarta and Bali in a total of 80 healthy individuals found that the most common genus was *Clostridium* followed by *Prevotella*, *Atopobium, Bifidobacterium*, and *Bacteroides*. [8] Looking further into the aforementioned study, it was reported that young individuals have more microbiota compared to those in the elderly. At the filum level, Rahayu ES found that *Firmicutes*, *Bacteroidetes, Actinobacteria,* and *Proteobacteria* are the dominating filum in healthy individuals. [8]

In the healthy intestine, gut microbiota may provide defense from pathogens by creating physical barriers or even by competing for nutrient sources. Several commensal bacteria may also produce metabolites, such as short-chain fatty acid (SFCA) which can directly inhibit the pathogenic bacteria. [9] SCFA consists of butyrate, propionate, and acetate which are nutrient sources for the host and have a role in anti-inflammatory response and cell proliferation. [3] Commensal microbiota can also produce vitamin K and abundant vitamin B which benefits the body.[3,9]

In the meta-analysis, Alvandi E et al found that the average of acetate, propionate, and butyrate in colorectal cancer was lower than in healthy individuals. [10] SCFA is produced by the gut microbiota through fiber fermentation. A high fiber diet is associated with the increment of SCFA level and has protective effect against the emergence of colorectal cancer. The study performed by Yusuf F in Indonesia also observed a similar result. [11] The average of acetate, propionate, and butyrate was lower in colorectal cancer patients, with statistically significant results in propionate and butyrate. [11] The association of SCFA and colorectal cancer can be explained as the high level of SCFA in the lumen can decrease the colon intraluminal pH which can inhibit the growth of pathogenic microbiota, such as *Enterobacteriaceae*. [11]

In the body's defense mechanism, as a response to pathogenic microbial infection or metabolites produced by pathogenic microbes, the body can secrete IgA. Differentiation and changes of B cells to plasma cells which can produce IgA are activated by several signals produced by gut microbiota. Commensal microbiota through its metabolite can also activate the differentiation of T-Reg cells. [9]

The balance between gut microbiota and the host immune system can be disrupted by the presence of pathogenic bacteria infection, disturbances, or decreases in the body's immune system. This will cause direct exposure of antigen or toxin to epithelial cells or immune cells which can cause inflammation and the initiation of tumour development. Several pathogenic microbiota can cause epithelial DNA damage and induce tumorigenesis through bacterial toxins being secreted. In a study in mice, several strains of E.coli can produce colibactin, a peptide-polyketides genotoxin, which can damage DNA and stimulate

tumour development.

The association between colorectal cancer and gut microbiota is a complex interrelated relationship and its pathogenesis requires a long time. Tumour development is initiated with chronic inflammation of the colon epithelial due to penetration of pathogenic microbes and/or toxins released by several pathogenic microbiota. Some intestinal microbiota then plays a role in advanced stages, such as the attachment of bacteria to the surface of the colonic mucosa, damage to epithelial DNA due to increased production of oxygen free radicals, and decreased antitumor T cell responses. *Fusobacterium nucleatum* may lead to the occurrence of colorectal cancer through E-cadherin/b-catenin signal modulation. [9] This modulation is performed by the adhesion protein, Fusobacterium adhesin A (FadA) which can activate the beta-catenin pathway.[6] Although several further studies are required to know the pathogenesis completely. [9] *Fusobacterium nucleatum* may cause the decline of antitumour T cell ability and increase NF-ƙβ expression which is responsible for tumour cell proliferation. Besides, Escherichia coli, a microbiota strain most common in the intestine, can cause the increment of oxygen free radicals and can secrete colibactin as has been explained previously. [6] In the final step, E. coli can also induce the synthesis of Hepatocyte Growth Factor (HGF). [6] HGF is one of the most common cytokines responsible for the tumour cell growth. [6]

The association between the pathogenesis of microbiota and colorectal cancer has been studied in vitro studies. Sunny et al performed a study in animals, in which both groups of animals were given faecal components from colorectal cancer patients, and the control group was given faecal material from healthy individuals. In the development of the studies, animals that received the faeces of colorectal cancer patients were found to have had hyperplasia polyps and microscopic polyps with cell proliferation. This study proved the association of faecal bacteria with the occurrence of carcinogenesis and colorectal cancer development. [12]

Besides pathogen microbes which can induce the development of tumour, several intestinal commensal microbiota play the opposite role, particularly inhibiting and preventing tumour development. *Faecalibacterium prausnitzii* can reduce the activation of the NF-ƙβ pathway in experiments in animals. [13] *Lactobacillus rhamnosus* GG and *Bifidobacterium lactis* can inhibit the proliferation of abnormal epithelial in patients with a history of polyps and can maintain and strengthen the physical barrier of the intestine. [14] In experimental animals, it was assumed that

Lactobacilli and Bifidobacteria have a role in suppressing the progression and size of colorectal cancer. [15]

## Factors Influencing Composition and Diversity of Gut Microbiota

As has been mentioned previously gut microbiota consists of several microorganisms found in the digestive tract and has an important role in the digestion process, metabolism, and immune system modulation. Several factors may influence the composition and diversity of gut microbiota.

**1. Food**

Food is one of the factors holding an important role in the composition and function of microbiota. In a study, it was reported that the increment of microbiota diversity and several bacteria, such as *Bifidobacteria* and *Lactobacillus* is influenced by high-fiber and plant-based dietary patterns. [16] Meanwhile, the consumption of high-fat and animal-based protein will decrease the diversity of microbiota. [17] Furthermore, a high prebiotic diet is useful for microbiota development which is beneficial for the body. [18]

**2. Medicines**

The wide use of antibiotics, particularly the wide spectrum may affect the diversity and composition of gut microbiota. The use of wide-spectrum antibiotics in a study was described to cause an increased ratio of Bacteroidetes/Firmicutes. [19] Uncontrolled use of antibiotics may also cause decreased diversity of microbiota and commensal microbiota. [20] This composition and diversity changes may happen up to 1-1,5 months after the administration of antibiotics. [19] Non-steroid anti-inflammatory drugs are also associated with the changes in microbiota and physical barrier of the digestive tract. The use of proton pump inhibitors also influences the balance of gut microbiota. Floris Imhann et al in a study reported that the use of proton pump inhibitors caused a decrease in the diversity and increment in the *Enterococcus, Streptococcus, Staphylococcus genus,* and *Escherichia coli*. [21] The influence of medicines on gut microbiota is very important, as it may cause dysbiosis, and inflammation, and increase the fragility to infection. Besides medicines, probiotic consumption can influence the diversity and composition of good microbiota in the body, but its influence decreases if the consumption is ceased. [22]

**3. Sex**

The diversity and composition of microbiota are influenced by sex. The difference in alpha diversity in males and females is observed after puberty. [23] This is associated with hormonal changes. Several studies reported the presence of an association between estrogen and microbiota. D'Afflitto in his systematic review of 13 studies found that in healthy females, increased estrogen level was associated with the increment of *Bacteroidetes filum,* the decline in *Firmicutes filum*, and increased microbiota diversity. [24]

**4. Physical activity**

Regular physical activity and exercise have a good impact on the health of gut microbiota. Exercise can increase the diversity of microbiota, and repair digestive tract function. Studies stated that exercise can increase Short-Chain Fatty Acid (SCFA) production which is important in the metabolism, inflammation regulation, and immune system modulation. [25] Exercise, on the other hand, may also decrease systemic inflammation and free radicals which affects the composition of gut microbiota.

**5. Chronic disease and condition**

Changes in the composition and diversity of gut microbiota are also influenced by several chronic diseases and conditions, including obesity, diabetes, and Inflammatory Bowel Disease. [26] This mechanism is so complex, including the influence of the presence of chronic inflammation, oxidative stress, metabolism changes, and digestive tract barrier function changes.

## Association Between Composition, Abundance, and Diversity of Gut Microbiota in Various Taxonomy Levels and Colorectal Cancer

From some pieces of literature, it was known that there are differences in the composition and diversity of gut microbiota between colorectal cancer and non-colorectal cancer patients. Bamola et al in India in their study obtained that filum Bacteroidetes is significantly more common in colon cancer patients, while filum Firmicutes was more common in healthy individuals. Meanwhile, at the genus level, *Alistipes, Coprococcus, Dorea, Rhodococcis, Rubrobacter,* and *Thiobacilus* were only found in cancer patients and not in healthy individuals. [27]

Liu Wanxian et al in their study have found differences in the composition and diversity of gut microbiota in patients with and without colorectal cancer in various taxonomy levels. [28]

In the filum level, there were 3 main groups of bacteria, particularly Proteobacteria which increased significantly in colorectal cancer patients, while *Bacteroidetes* and *Firmicutes* are the most common in healthy individuals. [28] At the genus level, the dominant bacteria found in colorectal cancer were Bacteroides, unclassified bacteria, *Escherichia, Provetella, Sutterella,* and *Faecalibacterium* with the proportion of 39%, 17%, 15%, 8%, 4% and 4%.[28]

Other studies performed by Jiyoung Ahn found some differences from the study by Liu et al, particularly in the filum level, the abundance of Bacteroidetes was relatively higher in colorectal cancer patients (16.2% vs 9.9%), while Firmicutes was found to be less (74% vs 80.3%). (29) In *Firmicutes filum*, the greatest decline was found in Clostridia class and *Lachnospiraceae* family. Clostridia is one of the intestinal bacteria which can digest fiber and complex carbohydrate-producing butyrate which inhibit colon inflammation and carcinogenesis. Similar to other studies, Jiyoung Ahn also found an increment of Fusobacterium genus in colorectal cancer patients. Fusobacterium, is a negative Gram, anaerobic bacteria which may cause colitis and periodontitis. [29] *Fusobacterium* can multiply in colorectal cancer tissue and may influence several cancer development stages, such as triggering the proliferation of cancer cells, release from the immune system, and influencing the chemotherapy results. This *Fusobacterium* can be used as a potential marker or as a target therapy which is expected to influence the development of colorectal cancer. Furthermore, there is also an increment of *Atopobium* and *Porphyromonas* genus related to colorectal cancer. [29] *Atopobium* is a positive Gram, anaerobic bacteria related to Crohn's disease and may inhibit apoptosis of cancer cells in vitro. Meanwhile, Porphyromonas is more common in the mouth and digestive tract. [29]

Another study performed by Ashley Hibberd et al also reported the difference in the composition and diversity of microbiota in colorectal cancer patients. [30] In their study, *Fusobacteria filum* and *Fusobacterium genus* are the most common in colorectal cancer tissue specimens, in which the relative abundance reaches more than 7% compared to its abundance in non-cancer patients, particularly < 0.5%. [30] *Euryarchaeota filum* and *Methanobrevibacter genus* are also common in the biopsy specimens of colorectal cancer patients. It is of interest that *Peptostreptococcus,* is a microbe common in the faeces, mucosa, and even in the tumour tissue of colorectal cancer patients. [30]

Other study performed by Yusuf et al in Aceh also reported that the population of B*ifidobacterium*

*bacteria* was found to be higher in non-cancer patients. Yusuf et al stated that there was decreased or absence of Bifidobacterium bacteria in the faeces could be a marker of colorectal cancer. [11]

This difference in composition and abundance is similar to other studies, however, it is of interest that in their study Liu et al obtained the data that in patients with polyps, the bacterial composition and abundance are similar to colorectal cancer patients, but there was no significant difference with the composition that of normal individuals. [28] This supported the opinion that bacterial changes occur in the initial phase or precancerous lesion, which then triggers and initiates tumour development.

As has been explained above, the gut microbiota is a complex ecosystem in the human digestive tract. Several studies above reveal the association between composition, abundance, and diversity of microbiota with the occurrence of several diseases. Colorectal cancer is one of the diseases known to be associated with the aforementioned changes. Biological diversity plays a role in maintaining the stability of a good digestive tract ecosystem. [26]

The diversity of gut microbiota can be divided into two, namely alpha and beta diversity. Alpha diversity is the diversity of species in the local habitat of an individual. Alpha diversity is influenced by the richness and evenness index. The richness of the species shows the number of different species present in an environment. Higher alpha diversity shows more number of different species that stay and live in that particular environment. Alpha diversity is usually evaluated using an index, namely the Shannon and Simpson index. Shannon's index can assess the richness and evenness directly, while Simpson's index assesses the presence of dominance of particular species in the same habitat.

Besides alpha diversity, there is also beta diversity. Beta diversity shows the diversity of species among different environments or individuals. This beta diversity represents the variety of microbiota among several faeces specimens. This beta diversity is usually evaluated using a plot to see the concordance and discordance of microbiota composition between samples.

Several studies investigated the association between the diversity of gut microbiota and colorectal cancer. Researchers found that there was decreased diversity in colorectal cancer patients. [29] This result is similar to the study by Dongmei A et al, which reported that colorectal cancer patients had decreased alpha diversity compared to healthy individuals and patients with adenoma. [31]

Jiyoung Ahn et al studied 141 faeces, from which 47 faeces were obtained from colorectal cancer patients. [29] In their study, they obtained that the diversity in colorectal cancer patients is lower compared to non-colorectal cancer patients. The diversity here was shown by the number of taxa found in the faeces. In further studies, Jiyoung reported that although there was a difference in the diversity, they did not find a difference in taxa evenness or distribution in every sample. Liu W et al performed a study involving 4 groups, namely colorectal cancer, polyp, adenoma polyp, and healthy individuals. From their study, it was described that there was a significant difference in the number or density of microbiota, particularly 271.9±58.6; 238.4±70.1; 240±63.2, and 265±80.7 in the normal, polyp, adenoma and colorectal cancer groups. [28] whereas there was no significant difference in the Shannon and Simpson index.

The identification of diversity patterns of microbiota is important in regards to the management of colorectal cancer. Gopalakrishnan et al in their study found that the diversity of microbiota is related to immunotherapy success. [32] This explained that intervention may modulate microbiota in the digestive tract and potentially increase the efficacy of colorectal cancer therapy.

## The Role of Microbiota as a Screening, Diagnosis, and Therapy Tool in Colorectal Cancer

From the aforementioned discussion, it could be implied that there is an association between gut microbiota and colorectal cancer. Microbiota has a role either in the initiation or progression of colorectal cancer. Therefore, knowing the diversity and composition of microbiota is expected to help us in performing screening or diagnosis of colorectal cancer.

There were several studies abroad that conducted diagnostic research on colorectal cancer using microbiota. Jessie Qiaoyi et al performed a study to evaluate the role of microbiota in colorectal cancer diagnosis in 676 subjects, which consisted of colorectal cancer, adenoma, or non-neoplasma patients. In the study, Jessie used 4 bacterial species, namely *Fusobacterium nucleatum*, *Lachnoclostridium sp. M3*, *Bacteroides clarus*, and *Clostridium hathewayi*.[33] Diversity of the those four bacteria is collected in a score named 4Bac which is then followed by diagnostic evaluation. In asymptomatic patients, 4Bac is more sensitive than Faecal Immunochemical Test (FIT) in

diagnosing colorectal cancer and advanced adenoma ($p< 0.001$), but has lower specificity compared to FIT (83.3% vs 98.6%). A combination of 4Bac and FIT may increase the sensitivity of the examination. (33)

Another meta-analysis by Huarong Zhang et al also observed a similar result. In their study, they reported 6 genera commonly identified as main markers in colorectal cancer. [34] Those six genera were *Anaerostipes, Porphyromonas, Fusobacterium, Parvimonas, Peptostreptococcus,* and *Gamela*. The combination of those six genera showed a diagnostic rate with a mean AUC of 0.76 in different studies. Further analysis using 3 main genera, particularly *Porphyromonas, Parvimonas, and Peptostreptococcus;* this model was able to differentiate colorectal cancer patients from normal individuals and those with adenoma with an AUC of 0.87 and 0.67. [34]

Besides being used as a diagnostic tool, gut microbiota can also be used as a biomarker in early detection of colorectal cancer. This can be seen in the systematic review performed by Florine H et al. The diagnostic ability of AUC of the gut microbiota as a precursor lesion biomarker, such as adenoma varies from 0.28-0.98. [35] Meanwhile, its diagnostic ability in detecting early-stage of cancer obtained an AUC of 0.65-0.93. (35) Therefore, the use of gut microbiota as a biomarker, either precancerous lesion or early detection of colorectal cancer is quite potential to be expanded.

The definitive management of colorectal cancer to date is still the same, particularly operation, chemotherapy, or even radiation, including the use of immunotherapy. Gut microbiota is currently known as one of the predictive factors of systemic treatment success in colorectal cancer patients. Gut microbiota may mediate immunomodulation response, and regulate metabolism, and play a role in the occurrence of chemotherapy resistance. Gut microbiota can also influence chemotherapy response. This influence can be seen in the administration of irinotecan, oxaliplatin, and 5-fluorouracil which are chemotherapy agents used in colorectal cancer. [3]

Microbiota dysbiosis may cause increased adverse effects of cancer treatment, such as irinotecan. Dysbiosis leads to the metabolic conversion of irinotecan which manifests as diarrhoea. Other cytotoxic drugs, including fluoropyrimidine also commonly prescribed to colorectal cancer patients, are also influenced by several gut microbiota. [3] Abundance of Fusobacterium nucleatum is inversely correlated with chemotherapy response of 5-FU. F. nucleatum can stimulate TLR4 and Myd88 and disrupt apoptosis, causing chemoresistance.[6]

In colorectal cancer patients with microsatellite instability who were given immunotherapy, changes in the composition and abundance of microbiota can influence the effectivity and increase the side effects. This effect is affected by the type of bacteria being present. Gopalakrishnan et al in their study of melanoma patients found that in the administration of PD-1 immunotherapy, effectivity is related to the increment of *Faecalibacterium* and *Ruminococcaceae*.[32] Gut microbiota may modulates immune system in colonic mucosa. This can increase the efficacy of immunotherapy by increasing the activity of CD8+ T cells or through the increased production of SCFA. (6) Preclinical studies showed that Bifidobacterium bacteria can increase the number of dendritic cells and CD8+ T cell infiltration to the tumour environment thus increasing the efficacy of immunotherapy. [3]

## CONCLUSION

Gut microbiota has several functions in maintaining the health of the digestive tract. Its changes may cause the occurrence of several disturbances which may trigger malignancy. Gut microbiota is local and specific, also influenced by several factors. The identification of gut microbiota patterns is very important in the diagnosis and management of colorectal cancer.

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