Review Article

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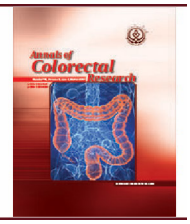

Systematic Review of Fecal and Mucosa-Associated Microbiota Compositional Shifts in Colorectal Cancer

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Abstract

Context: Gut microbiota fulfill a vital role in colorectal cancer. The aim of this study was to systematically review all the existing literature on the association of mucosa-associated and fecal microbiota with the incidence, location, and stage of both colorectal adenoma and carcinoma.
Acquisition Evidence: The scientific search was conducted up to July 2018. Among a total of 616 articles, 54 fulfilled the inclusion and exclusion criteria and were reviewed. The Newcastle-Ottawa Scale (NOS) for surveying the standard was utilized for quality control.
Results: A total of 54 articles were incorporated in the study. Fusobacteria 39 (72%), Firmicutes 22 (40%), Bacteroidetes 19 (35%), Proteobacteria 15 (27%), and Actinobacteria 10 (18%) were the most prevailing phylum that were found in colorectal cancer patients. Among these taxa, some of them grew more in colorectal cancer patients in contrast with the control; conversely, some taxa such as *Collinsella*, *Pedobacter*, *Bifidobacterium*, *Megamonas*, *Brevundimonas*, *Burkholderia* were less prevalent in colorectal cancer patients. Moreover, in some taxa like *Prevotella*, *Alistipes*, *Lachnospiraceae*, *Subdoligranulum*, *Roseburia*, *Ruminococcus*, *Eubacterium*, *Dorea*, *Bacillus*, *Parvimonas*, *Faecalibacterium*, *Dialister*, *Staphylococcus*, *Lactobacillus*, *Enterococcus*, *Blautia*, *Escherichia coli,* and *Pseudomonas,* there have been controversies among specialists.
Conclusion: Until now, several studies have incontestably reported the potential role of gut microbiota to be used for the detection of colorectal cancer; however, there are no predefined protocols. In this article, we attempted to summarize and organize articles that have investigated the microbiota as a type of strategy for screening colorectal cancer.

Keywords: Colorectal cancer, Colorectal neoplasm, CRC, Screening, Microbiota

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Introduction

Sporadic colorectal cancer (CRC) is the third cause of cancer mortality worldwide and one of the cancers for which population-based screening has effectively reduced mortality in the average-risk population (defined as asymptomatic individuals above 50 years of age without a personal or family history of increased risk of CRC) (1). Currently, the recommended screening modality for the average risk population is detecting the fecal occult blood (2).

In positive cases, the fecal immunochemical test (FIT) followed by colonoscopy is currently the standard noninvasive screening test. Although sufficiently sensitive, FIT lacks specificity, especially for the detection of non-advanced tumors. Furthermore, there is a rising trend in the incidence of sporadic CRC in young adults (<50 y/o) who are not targeted by existing screening recommendations (1). As a result, the younger population suffers from a higher stage of disease at diagnosis, and thus higher mortality rates (3). Despite the significant improvement in our understanding of the molecular pathophysiology of sporadic CRC, the knowledge has not been translated efficiently into early detection strategies. There is a growing need for developing non-invasive, targeted, and precise screening assays, especially for non-advanced CRC (2). To achieve better screening methods starting at an earlier age, we need a better understanding of disease pathogenesis, which could provide us with biomarkers for use in "at-risk" individuals.

Gut microbiota comprise a major component of the intestinal luminal environment and play an important role in colorectal cancer (4). Furthermore, microbes and microbiota can alter the balance of host cell proliferation, guiding immune system function or modulating the mucosal immunity, and thereby affecting intestinal epithelial proliferation and differentiation. Furthermore, with the biosynthesis of genotoxins, the microbiota can interfere with the cell cycle regulation and induce mutagenesis through the activation of dietary heterocyclic amines, acting as the metabolic link between cancer-associated gut microbes and fat- and meat-rich diet; there is also an association between the microbiome choline metabolism and CRC. Hence, microbiota may be a plausible link between the environment and CRC. Significant work is ongoing to understand how the role of the microenvironment (including the gut microbiome) influences immune-evading mechanisms or immune-editing in CRC, which should help unlock the potential of immunotherapy in this disease (5, 6)

Millions of microbiota exist in the gastrointestinal tract. They can be classified into four main categories: Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria (7, 8)

Fusobacterium nucleatum (Fn) is the best-studied bacterium in relation to CRC. It has consistently been more abundant in CRC compared with healthy controls, demonstrating tumorigenic potential in vitro. Given the higher abundance of Fn in CRC, non-invasive screening methods targeting Fn have been developed. Generally, the detection of Fn by quantitative PCR has a higher sensitivity and specificity compared to FIT; while the combination of quantitative PCR and FIT offers the best performance (4). However, Fn is absent in ~50% of CRC cases depending on the molecular subtype of CRC (5) and thus cannot be a sensitive and/or specific biomarker for CRC screening. It is plausible that taking other members of the gut microbiota into account could significantly improve the efficacy of microbiome-based CRC screening, as shown in a previous study (6). There is a need for identification of potential discriminatory bacteria and the development and validation of a clinically applicable multi-target microbiome assay.

Therefore, our objective was to systematically review all the existing literature on the association of mucosa-associated and fecal microbiota with the incidence, location, and stage of colorectal adenoma and carcinoma; this was done in an effort to investigate the microbiota as a kind of method for screening colorectal cancer.

Methods

Search Strategy

First, the authors wrote a protocol and a guideline was prepared so that every step was completed according to the protocol. Patients included people who had CRC and controls were defined as asymptomatic controls, symptomatic controls, and patients with adenoma (advanced or non-advanced adenoma), adjacent normal tissue, nontumoral lesions or polyps.

To achieve maximum search sensitivity and identify all studies that have investigated the relationship of CRC with microbiota, two steps for searching were used including an initial general search followed by a specific search. For the general phase, we searched the *Medline/PubMed*, *Scopus*, *ISI Web of Science*, *Science Direct*, *Embase*, *Cochrane Library*, *ProQuest*, *CINAHL*, *DOAJ*, *OVID*, *Wiley*, *EBSCO*, and *Google Scholar* databases for literature published up to July 2018. The search was limited to the English language. To accomplish maximum sensitivity of the search strategy and retrieve all studies, the following terms were combined: ("colorectal or colon or rectal, large intestine or large bowel" and "neoplasmor tumor or carcinoma or cancer" and "flora or microflora or microorganism or microbiome or microbiota or microbe or microbiology or germ or bacteria or bacterium or fungus"). In the specific search, each of those genera with CRC and their mesh terms were searched. In this stage, we found more than 616 articles. The search strategy is depicted in Figure 1.

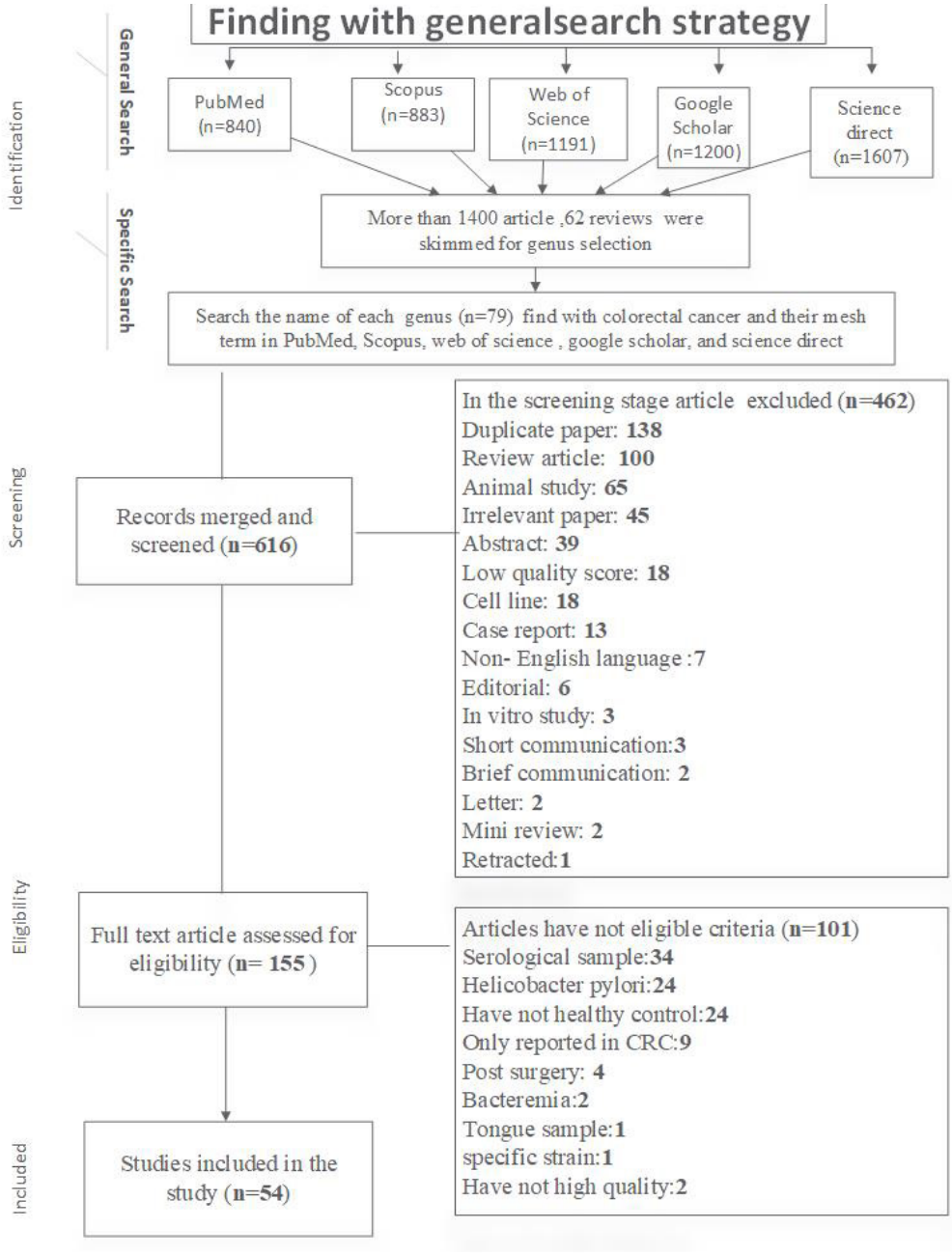

Figure 1: Flow-Diagram of Identified Studies

Selection Criteria

Studies providing the following criteria were considered for inclusion into the present research: 1) studies that were published in English; 2) studies that involved intestinal flora culture and/or sequencing on stool or tissue samples. Exclusion criteria were as follows: 1) letters, editorials, short correspondences, brief communications, case reports, review, mini-review, or conference reports; 2) studies on cell lines, tongue samples, or serological samples; 3) studies on specific strains, bacteremia, or *Helicobacter pylori*; 4) studies that did not have healthy controls or only reported CRC. Two reviewers (M.M. and Z.K.) independently scanned the titles of all retrieved articles, removed duplicates, and identified potentially relevant abstracts for further assessment. For further evaluation of relevancy and refinement, two researchers independently reviewed the selected abstracts. In the case of a disagreement between the reviewers, two other researchers (Z.M. and F.B.) acted as mediators.

Quality Control

We used the Newcastle-Ottawa Scale (NOS) for assessing the quality of studies included into the present meta-analyses scale to assess independently the methodological quality of a clinical trial, ranging from a score of 0 to 5. The studies that met at least five NOS criteria were considered high-quality studies. The minimum score for this study was 3 out of 5. For extracting data from the articles, each author independently used a form and a checklist. Then, the authors double-checked the data with each other.

Method for Identification

For the identification of microbiota in CRC,

researchers have used various ways such as fluorescence in situ hybridization (FISH), quantitative real-time polymerase chain reaction (qPCR), droplet digital polymerase chain reaction (ddPCR), and fluorescent quantitative polymerase chain reaction (FQ-PCR). In addition, investigators have used several different methods for sample collection including formalin fixed paraffin embedded (FFPE) CRC tissues, CRC frozen tissues, genomic DNA, and feces collected from CRC patients.

Results

Finally, 54 articles were entered into the study. The most studied phyla were Fusobacteria (39 studies; 72%), Firmicutes 22 (40%), *Bacteroidetes* 19 (35%), Proteobacteria 15 (27%), and Actinobacteria 10 (18%) were the most prevalent phyla that were found in CRC patients. Among these taxa, some of them were more prevalent in CRC patients compared with the control; on the other hand, some taxa like *Collinsella*, *Pedobacter*, *Bifidobacterium*, *Megamonas*, *Brevundimonas*, and *Burkholderia* were found less in CRC patients. Besides this, in some taxa such as *Prevotella*, *Alistipes*, *Lachnospiraceae*, *Subdoligranulum*, *Roseburia*, *Ruminococcus*, *Eubacterium*, *Dorea*, *Bacillus*, *Parvimonas*, *Faecalibacterium*, *Dialister*, *Staphylococcus*, *Lactobacillus*, *Enterococcus*, *Blautia*, *E. coli*, and *Pseudomonas*, there were controversies among articles. In the following paragraphs, detailed information is presented.

1. Fusobacteria

Fusobacterium is a genus of obligatory anaerobic filamentous gram-negative rods that are members of the phylum Fusobacteria. *Fusobacterium* is reported in this section because it can promote the development of CRC (9). Several mechanisms have been proposed for the induction of CRC by *Fusobacterium*, including the augmentation of inflammatory cytokine levels in a pro-inflammatory microenvironment that accelerates the progression of colorectal tumors, the interaction of FadA with E-cadherin on epithelial cells and promoting tumor cell proliferation, blocking the cell cycle and attracting myeloid-derived suppressor cells, and generating a tumor-immunosuppressive microenvironment that promotes colorectal tumor progression (10). We found 39 related articles, among which 21 were performed on tissue samples and the remaining examined stool samples. Except for three studies, the remaining showed that *Fusobacterium* count was boosted in CRC patients, but conclusive results could not be obtained due to a wide range of individuals and research groups with varied methods and samples. In 24 articles, the number of *Fusobacterium* was significantly higher among patients with CRC than the controls (P<0.05) (11-31). In one study, *Fusobacterium* was higher in the controls, which included patients with normal colonic mucosa, adenomas, and non-adenoma, and 16S rRNA genes were used to characterize adherent bacteria. Although in most studies the cases had higher bacterial diversity and richness than the controls, one study revealed that *Fusobacterium* spp. was present only in the control group (32). Moreover, two studies showed no differences between cases and controls (33, 34). J. Goedert's study examined the fecal sample of the normal group (NG), colorectal adenoma (CRA) patients, and CRC patients. They showed that the relative abundance of Fusobacteria taxa was non-significantly lower in CRA cases than in the NG (0.4 vs. 1.0%, P=0.46) (33). In another study, the bacterial profile of normal tissue (NT) was determined with 16S rRNA, revealing no differences in the abundance of Fusobacteria between the CRC, NG, and advanced adenoma (AG) groups. The researchers stated that studies on the specific gut microbiome compositions and profiles associated with CRC or AG have shown inconsistent results (34). Another study showed an increasing trend of *Fusobacterium* spp. in tumors of patients (87.5%), although no significant results were discovered (35).

1.1 Tumor Tissue

1.1.1 Relative Abundance

Some articles reported Fusobacteria and their genera with relative abundance in tumor, mucosa, adenoma or adjacent NT samples. In most articles, the percentage of Fusobacteria or their genera in the CRC was higher in comparison with the respective NGs, varying between (0.01% to 10.8%) for *Fusobacterium* spp., while the relative abundance of other genera are higher and variable (30.3% to 77.6%). For example, one study reported that Fusobacteria were present in 17% of cancer patients, 9.57% of NG, and 5.22% of the AG (11). The relative abundance of the *Fusobacterium* spp. was also reported in that work (14.52% in CRC, 9.39 % in NG, and 3.12% in AG) (11). *Fusobacterium* spp. have shown higher relative abundance in tumors with more than (50%) circumferential involvement (26). Furthermore, the rate of *Fusobacterium* spp. presence was 10.08% in CRC vs. 0.01% in the NG of another study, revealing a significant relationship (36). In another study, *Fusobacterium* spp. constituted less than 0.1% of total bacteria in the NG and were most prevalent in the mucosa of patients with CRC (10.08 vs. 0.01%) with significant differences between the groups (37), Furthermore, the *Fusobacteriaceae* family showed matching differences (3.72% CRC patients vs. 0.18% NG, P=0.045) (38). In a separate study, Fusobacteria in the CRC group were present in 10.58% of cases compared with 0.03% in the NG (P<0.001) (36). Among the 25 tumor-normal paired tissue samples, eight CRCs (32%, four right and four left), but not their paired surgically resected NT, were Fusobacteria-dominant in one report (39). It has also been expressed that Fusobacteria (8.80 vs. 4.28%,

P=0.0031) were detected at higher percentages in tumor tissue (TT) than in the adjacent mucosa (40).

The relative abundance of other genera is higher than Fusobacteria and their *Fusobacterium* genera. For example, in one study that included 149 participants, *Fusobacterium nucleatum* and *Pan-fusobacterium* were detectable in 78 (52.3%) NG individuals and 110 (73.8 (% CRC patients, while 111 (74.4%) had either Fn or *Pan-fusobacterium*. Among 89 adjacent NT samples, Fn and Pan-fusobacterium were detectable in 27 (30.3%) and 47 (52.8%) for the NG and CRC groups, respectively (41). On the other hand, *Fusobacterium* spp. was detected in 72.16% of tumors and 67.01% of adjacent tissues (14). In one Chinese study, the authors stated that Fn was identified in 118 of the 152 (77.6%) tumor tissues (TT) and in 87 of the 152 (57.2%) matched NTs (P<0.001) (24). The infection rate of Fn in CRC tissues is reportedly significantly higher than that in adjacent NT (77.6 vs. 57.2%, P<0.001) (25).

1.1.2 Mean Abundance

We changed the median abundance of some papers to mean abundance to achieve greater homogeneity of data based on the predefined formula. Zhou et al. found that the mean abundance of CRC tissue is 0.23±0.20 compared to adjacent NT (0.04±0.20, P<0.01) (13). In the total of 280 pairs of tumor and adjacent NT collected from stage III/IV CRC patients who underwent surgery, the median abundance in TT was 0.10±0.21 and in NG was 0.02±0.05 (P<0.001) (42). In Warren's study, 65 controls and 65 tumors were compared, showing that the mean abundance of *Fusobacterium* in the NG was 1.36±0.45 in comparison with 4.89±1.11 in the CRC group (P<0.002) (18). The abundance of *Fusobacterium* spp. was significantly higher in AG compared to NG (mean log copy number and standard error, cases: 8.44±0.38; controls: 7.40±0.22, P=0.01) (23). Fusobacteria were compared between US and Spain participants with adjacent (8.1±19.8) and TTs (8.4±16.3). Moreover, Spain's participant had values of 1.6±4.2 in adjacent tissue and 10.5±14.6 in TT (29).

1.1.3 Enrichment

Some of the articles did not describe relative or mean abundance, but rather presented the P-value for enrichment of *Fusobacterium* spp. in CRC cases relative to NGs (e.g., Alomair's study; P=0.007) (16). Relative quantification of Fn was significantly raised in the TT compared to the matched NT in all three European cancer cohorts (Czech Republic (CZ) cohort P=0.002; DE (Germany) cohort P=0.0001; IE (Ireland) cohort P=0.006) (24). In addition, one study showed that in the early-stage of CRC, *Fusobacterium* spp. were most significantly enriched (30). Furthermore, *Fusobacterium* spp. were significantly more abundant in a rectal cancer sample (43). Overrepresented species concern members of the *Fusobacterium* genera that are generally regarded as gut commensals with probiotic features (44).

1.2 Stool Sample

1.2.1 Relative Abundance

Like the previous report from mucosa and TT, the Fusobacteria as a whole have lesser relative abundance than *Fusobacterium* genera. Most articles showed significant results and the percentages varied between 0 to 10.58% for the NG and CRC groups. In addition to the tissue samples, other genera of Fusobacteria have higher relative abundance than *Fusobacterium spp.* In one study, a significantly higher proportion of Fusobacteria was observed in the carcinoma-in-adenoma group (4%) relative to the control group (0%; P<0.05) (45). In 40 participants who referred to the Chinese Academy of Medical Science, 20 CRC patients and 20 NG were selected. The CRC group (1.02%) had a marked increase in the relative abundance of Fusobacteria compared with the NG (0.47%; P<0.01) (20). Furthermore, another group reported that Fusobacteria were reported in 10.58% of CRC cases compared with the NG (0.03%; P<0.001) (37). In a different study, Fusobacteria constituted the next most dominant phyla, contributing to 2.81% of NG individuals and 4.68% of CRC patient s(46). J. Goedert showed that the mean relative abundance of Fusobacteria was 0.4% in the AG and (1.0%; P=0.46) in the NG (33). Moreover, at the genus level, *Fusobacterium spp.* were found in 0.004 % of the NG individuals compare with 3.84% in the carcinoma-in-adenoma patients of one study (45). Another report stated that the occurrence of *Fusobacterium spp.* in CRC was 98.2%, compared with 72.0% in the NG (P<0.0001) (21). Other researchers reported different rates of *Fusobacterium* spp., namely 10.08% in the CRC group compared with 0.01% in the NG (P=0.032) (37). On the other hand, other genera like *Fusobacterium* were not determined in the NG in comparison with carcinoma-in-adenoma patients. *Fusobacterium nucleatum*, which is known to be frequently detected in patients with CRC, was found in only one sample of a patient with sessile serrated adenoma (SSA). The percentage of Fn sequence was also very low in that sample (0.04%) (45). In accordance with the sequencing results, *F. nucleatum* was much more commonly found in the CRC group (45%) compared with all other groups (advanced AG: 28%; non-advanced AG: 24%; and NG: 30%; P=0.022), but no statistically significant differences in *Fusobacterium* spp. were found between advanced AG (n=113) and NG (n=231; P=0.802) or non-advanced AG (n=110) and NG (P=0.803) (47). *Fusobacterium nucleatum* was observed in more fecal samples from CRC patients compared to the NG of another research (60% vs. 22.2% ; P=0.07) (48).

1.2.2 Mean Abundance

In one study, it was shown that the CRC patients had 7.5±3.7 and NG had 5.6±3.6 mean abundance of

Fusobacterium spp. (20). *Fusobacterium* spp. have also been reported to have mean abundances of 1.24 and 7.36 in healthy and CRC patients, respectively (P=0.0034) (49). Feng et al. expressed the mean abundance in all control (0.0000000028), adenoma (0.0000000001), and carcinoma (0.00000015) patients (28). Moreover, another study found these figures at 0.08±0.1 in the CRC group and 0.0003±0.0009 in the NG group (P=0.0348) (29). Mean abundance value in NG is 1.24, whereas the mean abundance value in CRC patients is 7.36, according to a different report (P=0.0034) (49). The mean abundance of *Fusobacterium* spp. has also been found to be 2.59 in CRC patients compared with a NG (0.005) in another work (50).

1.2.3 Rank Mean

Similar to most of the aforementioned studies, the Fusobacteria and other genera were significantly more present in CRC patients than controls, and the rank mean of cases both in adenoma or carcinoma was significantly higher. Feng et al. study determined the *Fusobacterium* spp. oral taxon rank mean in a NG (54.03), AG (64.45), and CRC (95.41) group (28).

Likewise, another study showed that the *F. nucleatum* control rank mean was 45.09, compared with a case rank mean of 78.66 (P=0.0003). Furthermore, *Fusobacterium* spp. oral taxon control rank mean was 45.02 and the case rank mean was 78.70 (P=0.0004). Additionally, in *Fusobacterium necrophorum*, the control rank mean was (52.37) compared with a case rank mean of 73.35 (P=0.0003). For *Fusobacterium varium*, the control rank mean was 52.37, and the case rank mean was 73.35 (P=0.0003). Finally, the control rank mean for Fusobacteria was 44.68, and case rank mean was 78.95 (P=0.000000014) (51).

1.2.4 Enrichment

Fusobacteriaceae, the main component of the phylum Fusobacteria, are reportedly significantly enriched in CRC patients (P=0.001) (20). Among 203 CRC cases and 236 healthy subjects from two independent Asian cohorts, the control rank mean was 40.32 and the CRC rank mean was 82.14 (P<0.0001) for *Fusobacterium nucleatum* (21). In 42 CRC cases and 89 matched controls from the Sinha study, CRC was independently associated with higher levels of *Fusobacterium* spp. (22). The mean abundance of *Fusobacterium* spp. was significantly higher in patients with CRC than controls (P<0.001) (52). Both Chinese and French population showed increased Fusobacteria in CRC patients than controls (53). Relative to healthy subjects, subjects with carcinomas had higher abundances of OTUs associated with *Fusobacterium spp.* (54).

Based on our findings, numerous studies have provided functional evidence that helps to explain how Fn can progress cancer formation. However, until now our finding are limited, and further investigation to reduce the risk of Fn is needed. In summary, to enhance the prevention, diagnosis, and treatment of gastrointestinal cancer, the close relationship between Fn and gastrointestinal cancer is of great significance, comprising a worthy subject for further research.

2. Firmicutes

The Firmicutes are a phylum of bacteria that have Gram-positive cell wall structure and are the second most abundant bacterial phylum. Moreover, it is the most prevalent phylum that we found in the articles. At the phylum level, out of 54 articles we collected and studied, 22 articles reported data on Firmicutes from CRC patients and case-control individuals. The biopsies of 11 out of 22 studies included TTs. Among these 11 articles, six of them reported relative abundance, one of them reported mean abundance, and four of them reported enrichment. In addition, three articles reported P-values and only one of them reported the q exam. Among these 11 articles, five increases and four decreases in Firmicutes were reported. In Shen et al.'s study, there were no significant differences between cases and controls for the phylum of Firmicutes. In Allali et al.'s study, the mean abundance of Firmicutes was different between cases related to the US and Spain. The samples of 11 out of 22 studies were stool samples. Among these 11 articles, five of them reported relative abundance, two of them announced mean abundance, three of them disclosed enrichment, and one of them reported rank mean. Across all articles, five studies reported P-value. Five studies reported a higher rate of the mentioned phylum relative to the control. Furthermore, among families, species, and classes, the Peptostreptococcaceae was the most common family; this was reported in 16 articles, with an increased presence in CRC patients in all but one article (5). *Lachnospiraceae* was another common family, with higher and lower rates in CRC patients than controls in five and six studiesm respectively. However, one article showed non-significant results in this regard. Among the genera of Firmicutes, *Ruminococcus*, *Roseburia*, *Streptococcus*, and *Facecalibacterium* were extracted in 16, 14, 13, and 12 articles, respectively. Except for *Roseburia*, most of these taxa were elevated in CRC. In the species and the class level of Firmicutes, only three taxa were identified in the articles, the most important of which was *Blautia*. Totally, eight articles showed that the presence of this species of Firmicutes fell in CRC, but four described its growth. In conclusion, if we look at the table we know that in most articles this phylum and its taxa were more present in CRC patients except for the *Brochothrix* and *Megamonas* genera.

2.1 Tumor Tissue

2.1.1 Relative Abundance

In Sanapareddy's study, one of the three dominant phyla among adenoma cases was Firmicutes

(42.6%) (31). In another study, the population was comprised of 11 normal and 60 CRC patients who had undergone radical colectomy. In this study, the relative abundance of Firmicutes was 66.44% in the probiotic group, 60.97% in the perioperative placebo group, and 40.21% in the healthy volunteer group (P=0.019) (37). In addition, in one study, colorectal TT samples were obtained intra-operatively from recently diagnosed CRC patients. This included 31 cancerous tissues, 20 adjacent non-cancerous tissues, 15 proximal colon cancer tissues, and 16 distal colon cancer tissues, and, additionally, 30 corresponding colorectal mucosal samples of healthy volunteers. At the phylum level, Firmicutes were the most predominant phylum, contributing to 63.46% and 39.54% of the gut microbiota in cancerous tissues and adjacent non-cancerous tissues (P<0.001), respectively (36). In the Lu study on 31 patients with AG and 20 NG members, the bacterial flora analysis revealed that Firmicutes was the most predominant phylum, contributing to 53.7 and 88.6% of the tissue microbiota in colorectal adenoma patients and the NG individuals, respectively (34). In another study, tissue samples including tumor and adjacent NT were collected from 65 patients with CRC during surgery. At the phylum level, Firmicutes was the dominant phylum among other phyla, moreover, they were less frequent in tumors than in the corresponding NT (37.12 vs. 44.72%, P=0.0076) (40). In Xu and Jiang's study, they recruited 160 individuals from 61 cases with non-tumor colon regarded as the NG, 47 cases with histology-substantiated colorectal adenomas regarded as the AG, and 52 cases with invasive adenocarcinomas considered as the CRC group. In this study, Firmicutes was enriched more in the CRC (41.87%) patients compared with the NG (33.86%) and AG (32.44%) (11).

2.1.2 Mean Abundance

In a cohort study, twenty-two identified tumors and adjacent tissues were collected from the University of North Carolina (UNC) Tissue Procurement Facility and Spanish samples. In addition, CRC tissue from patients who underwent surgery in the Hospital Universitario Central de Asturias (HUCA), Spain were selected. The mean abundance of Firmicutes in this cohort study was 22.2±15.5 in adjacent tumor samples vs. 27.1±16.4 in tumor samples from the US and 43.9±18.3 in adjacent tumor samples vs. 36.8±18.4 in tumor samples from Spain (27).

2.1.3 Enrichment

In one study, the phylogenetic distribution of the bacteria phylotypes were identified among 142 clones from four controls and 200 clones from four cases, revealing a similar abundance of Firmicutes among CRC cases and controls (32). In Marchesi et al. study, six patients underwent resections for primary colon adenocarcinoma at the Radboud University Nijmegen Medical Centre. The data disclosed a general tendency of less Firmicutes in TT compared to matching off-tumor mucosa (44). In another study, excess colon, tumor (adenomas and cancers) and paired NTs were collected for analysis of patients undergoing surgery. Firmicutes was among the predominant bacterial phyla associated with adenomas and CRCs (39). In another study, mucosal biopsies were obtained from a total of 160 individuals with tumor-free colons (n=61) and confirmed histology of colorectal polyps (n=47) or invasive adenocarcinomas (n=52). Researchers of this study also recruited an independent cohort of 116 individuals of which 25 subjects had normal colons, 41 subjects had colorectal adenomas, and 50 subjects were diagnosed with CRC, from the Beijing Military General Hospital. Members from the Firmicutes phylum were more likely to form co-occurring associations with each other in ordinary colonic mucosae than lesions and lesion-adjacent samples. These outcomes indicate that members from the gut microbiota can shape specially explicit connections, which might be a reaction to an altered colonic mucosal microenvironment or could be one reason for the ailment state (30).

2.2| Stool Sample

2.2.1 Relative Abundance

In the other study, 46 CRC samples and 56 NG samples were acquired. All patients were categorized according to histopathological features by TNM classification of malignant tumors after surgery. Among all bacterial groups revealed by the interpretable sequences, Firmicutes was the most predominant phylum, contributing to 63.1 and 57.2% of the gut microbiota in CRC patients and NG volunteers, respectively (46). In another study, a total of 46 CRC patients and 56 NG individuals were selected. One of the three dominant phyla among CRC cases was Firmicutes (50.82% in cancerous tissue vs. 77.59% in the intestinal lumen; P=0.001) (38). In another study, at the phylum level, 10 phyla presented in all of the samples and Firmicutes was one of the most dominant phyla. On the other hand, the rate of Firmicutes presence was 36.6% among CRC patients and 38.9% in the NG (20). In a study, a total of 15 patients with CRC (nine males and six females) and 12 NG controls were selected by researchers. In this study, the dominant bacterial phylum in samples from both groups were Firmicutes (44.0%) in the CRC group vs. 40.9% in the NG; P>0.05 (49). In another research that was done on stool samples, the relative abundance of Firmicutes was obtained as follows: CRC=50.5% vs. NG=28.4% (P<0.05) (29).

2.2.2 Mean Abundance

The mean abundance of Firmicutes in a cohort study was 1.77E-03 (CRC vs. neoplasia-free) (55). In addition, based on the study that was done at the Minhang and Xuhui district community health centers, the mean abundance of Firmicutes was

5.24E-01 in the control group and 4.68E-01 in the adenoma group was (P=0.32) (33).

2.2.3 Enrichment

Analyses of fecal samples have revealed that the human intestinal microbiota is dominated by Firmicutes, which is one of the dominant phyla that makes up more than 99% of the identified phylogenetic types, though the composition differs between fecal and mucosal communities. The comparative metagenomics approach with human fecal samples has indicated that the complexity of Firmicutes is reduced in Crohn's disease patients compared with NG controls (56). In the Kasai study, analyzing fecal samples showed that Firmicutes was one of the most dominant phyla among carcinoma-in-adenoma subjects (45). In a cohort study for the gut microbiome structure, the population showed an increased ratio of two dominant bacterial divisions in CRC patients, one of which was Firmicutes (53).

2.2.4 Rank Mean

In a cohort study, fecal samples were accumulated from 74 patients with CRC and 54 controls from China, with the outcomes being validated using data related to 16 patients and 24 controls from Denmark. The mean rank of Firmicutes in this study was 57.97 in the CRC patients and 73.44 in the NG (P=0.029) (51).

Firmicutes, like Fn, were overrepresented in most articles, and Firmicutes was one of the most prominent phylum. Also, this phylum was significantly more abundant in the gut microbiota of cancerous tissues than that of adjacent non-cancerous tissues. In summary, Firmicutes, as part of the gut microbiome, is involved in energy resorption and its members are highly diverse in terms of phenotypic characteristics. Members of the phylum display a disparate distribution in which some species are enriched in the TTs whereas others inhabit healthy gut. Therefore, this taxon appears to be one of the remarkable indices for screening of CRC.

3. Bacteroidetes

The phylum Bacteroidetes is composed of three large classes of Gram-negative, non-spore-forming, anaerobic/aerobic bacteria, highly abundant in the intestines. They perform essential metabolic conversions, such as the degradation of proteins or complex sugar polymers.

Among 54 articles that we collected and studied, 19 articles reported Bacteroidetes data from case-control studies. The biopsies of 10 out of 19 articles were TT, among which seven reported relative abundance. One of them reported mean abundance and two articles reported enrichment. Six out of 10 articles showed a higher Bacteroidetes prevalence among CRC patients and others yielded the converse result. Moreover, four of the studies reported P-values. The samples of 9 out of 19 studies were stool samples; five of these nine studies reported relative abundance. In addition, one of them reported mean abundance and three articles reported enrichment. Finally, 7 out of 9 articles revealed higher rates of Bacteroidetes among CRC patients; others indicated a decreased amount of Bacteroidetes. Three articles reported P-values.

Prevotellaceae was the most prevalent family of this phylum that revealed an increasing trend in CRC patients who entered into these studies. On the species level, *Porphyromonas* was another taxon, which disclosed growth in CRC patients except one of them (7). By and large, we can conclude that most of the taxa in this phylum indicated a growth effect on CRC patients.

3.1 Tumor Sample

3.1.1 Relative Abundance

In one study, analyzing CRC cases and controls showed that Bacteroidetes members were less abundant in cases (29.14%) compared to controls (37.24%; P<0.05) (32). In another study, one of the three dominant phyla among adenoma cases was Bacteroidetes (25.5%) (31). The data from another research showed that the relative abundance of Bacteroidetes was 8.49% in the Probiotic group, 10.12% in the perioperative placebo group, and 11.06% in healthy volunteer group (P>0.050) (37). In the other study at the phylum level, after Firmicutes, Bacteroidetes was the most predominant phylum, contributing to 12.77 and 19.1% of the gut microbiota in cancerous tissues and adjacent non-cancerous tissues, respectively (P>0.05) (36). In another research, the third most dominant phyla in colorectal adenoma patients was Bacteroidetes (10.8%), but there was a clearly lower relative abundance of this phylum in the NG (5.8%) (34). In the study of Gao at the phylum level, the relative abundance of Bacteroidetes was 27.66% in tumor samples vs. 23.82% in adjacent normal mucosa (P>0.05) (40). In a final study, the relative abundance of Bacteroidetes was 17.31% in CRC; 16.61% in AG and 16.60% in NG (11).

3.1.2 Mean Abundance

The mean abundance of Bacteroidetes in a cohort study was 55.5±22.1 in adjacent tumor samples vs. 54.5±19.0 in tumor samples in the US and 46.6±19.5 in adjacent tumor samples vs. 45.5±16.8 in tumor samples in the Spanish population (27).

3.1.3 Enrichment

The data analyses of six patients in the Marchesi study showed a general tendency of more Bacteroidetes in TTs in comparison with matching off-tumor mucosa (44). One of the predominant bacterial phyla associated with adenomas and CRCs is Bacteroidetes (39).

3.2 Stool Sample

3.2.1 Relative Abundance

Among all bacterial groups revealed by the

interpretable sequences, the relative abundance of Bacteroidetes contributed to 22.7 and 32.0% of the gut microbiota in CRC patients and NG controls, respectively (46). One group reported that one of the three dominant phyla among CRC cases was Bacteroidetes (26.37% in cancerous tissue vs. 13.68% in the intestinal lumen, P=0.002) (38). In Wu's study, 20 CRC patients and 20 control cases were selected. Through biopsy analysis, the data showed the relative abundance of Bacteroidetes contributed to 56.5% in the CRC group and 53.9% in NG (20). In another study, after Firmicutes, the dominant bacterial phylum in samples from both groups was Bacteroidetes (35.6% in the CRC patients and 47% in the healthy control group; P>0.05) (49). In Allali's study, fecal samples were obtained from 11 CRC patients and 12 healthy subjects. In this research, Bacteroidetes were more prevalent in controls than in CRC patients (35.1%; P=0.06) (29).

3.2.2 Mean Abundance

The mean abundance of Bacteroidetes in a cohort study was 9.49E-02 (CRC vs. neoplasia-free) (55).

3.2.3 Enrichment

In Goedert's study, one of the most common phyla among CRC patients was Bacteroidetes (33). Fecal sample analysis of patients who were under 65 demonstrated that the composition and relative abundance of the major bacterial phyla were similar, with Bacteroidetes being one of the dominant phyla (45). In another study, 52 patients were enrolled in the negative control group, 47 patients in the colorectal adenoma group, and 42 patients in the CRC group. In this cohort study for the gut microbiome structure, the population disclosed an increased ratio of two dominant bacterial divisions in CRC patients, one of which was Bacteroidetes (53).

In summary, based on the current knowledge, it is quite difficult to define the accurate impacts of microbiota like Bacteroidetes on CRC, but it seems that Bacteroidetes may be involved in immune modulation like activation of inflammation and autoimmune disease. Therefore, we can investigate the effect of this taxa on CRC, and future studies may show the accurate pathway for the mechanism of this genera in possibly promoting CRC.

4. Actinobacteria

The Actinobacteria are a phylum of Gram-positive bacteria. They can be terrestrial or aquatic. Among 54 articles which were collected and studies, 10 reported Actinobacteria. The biopsies of 6 out of 10 studies were TT, and 3 articles showed an increasing trend in Actinobacteria among CRC patients; however, 3 articles showed a decreasing trend in Actinobacteria. In addition, 3 out of 6 articles had reported the P-value. The samples of 4 out of 10 studies included stool samples and two articles showed a higher rate of Actinobacteria among CRC patients. One article clarified a decreased trend and another study showed no significant difference. The most important family of this phylum was *Propionibacteriaceae*, which declined in most articles. *Bifidobacterium* was a genus of this phylum that illustrated non-significant differences between CRC patients and NG. Among most articles, a lowered rate was evident for this genus. On the other hand, *Actinomyces spp.* were more prevalent in CRC patients in all the aforementioned articles except one (28). At the species level, *Micrococcus* and *Atopobium* were less and more in CRC patients, respectively. We did not find any class level for this phylum.

4.1 Tumor Sample

4.1.1Relative Abundance

The data of one study illuminated that the relative abundance of Actinobacteria was 2.58% in the probiotic group, 1.46% in the perioperative placebo group, and 1.91% in the NG (P>0.050) (37). In another study, Actinobacteria was the last predominant phylum among other phyla, contributing to 1.46% and 3.48% of the gut microbiota in TTs and adjacent non-cancerous tissues, respectively (36). In Gao's study, at the phylum level, the relative abundances of Actinobacteria was 1.01% in tumor samples vs. 1.37% in adjacent normal mucosa (P=0.025) (40).

4.1.2 Mean Abundance

In Allali's cohort, the mean abundance of Actinobacteria was 0.5±0.3 in adjacent tumor samples vs. 0.5±0.4 in tumor samples in the US and 1.6±1.8 in adjacent tumor samples vs. 1.7±2.0 in tumor samples among the Spanish population (27). In another study, the mean for the control group was 2.15 and the mean for the case group was 2.22 (P=0.31) (31).

4.1.3 Enrichment

In a study, tissue specimens were collected from 36 subjects (18 non-cancer subjects and 18 rectal adenocarcinoma subjects). Researchers observed a significant difference in the log abundances of Actinobacteria between the non-cancer (2.1) and rectal adenoma (2.6) groups (P<0.001) (43).

4.2 Stool Sample

4.2.1 Relative Abundance

Among all bacterial groups revealed by the interpretable sequences, the relative abundance of Actinobacteria contributed to 4.55 and 2.22% of the gut microbiota in CRC patients and healthy volunteers, respectively (46).

4.2.2 Mean Abundance

The mean abundance of Actinobacteria in a cohort study was 4.58E-02 in the CRC cases vs. neoplasia-free controls (55).

4.2.3 Enrichment

In Wu's Study, no significant differences were observed between the healthy subjects and CRC patients for Actinobacteria (20). In Zeller et al.'s cohort study, Actinobacteria significantly decreased in CRC patients. In another cohort study, the population under study showed an increase in Actinobacteria in CRC patients (53).

In comparison to the previous taxa, there were limited studies assessing the effects of Actinobacteria on CRC. Therefore, it seems that we cannot define the accurate mechanisms of this microbiome for its potential effects on CRC. In addition, the current published articles have heterogeneous results; future studies may be needed to achieve better conclusions.

5. Proteobacteria

Proteobacteria is a major phylum of Gram-negative bacteria. It makes up one of the largest and most versatile phyla in the Bacteria domain. Between 54 articles, we collected and studied 15 articles that reported Proteobacteria data from CRC patients and case-control individuals. The biopsies of 9 out of 15 studies were TTs, and two out of 9 studies uncovered that Proteobacteria was more prevalent among CRC patients. In addition, 6 articles showed a decreased trend in Proteobacteria and only one study showed no significant difference. However, 5 out of 9 studies had reported P-values in their articles. The samples of 6 out of 15 studies were stool sample; 5 out of these 6 studies exhibited a higher rate of Proteobacteria among CRC patients, and only one showed no significant difference. We did not observe any lower rates of this phylum among CRC patients. Two out of 6 studies had reported P-values in their articles. *Enterobacteriaceae* is the most important family of this phylum; this family had a stronger presence among the CRC patients than the controls. Because of the versatility of this phylum, we encountered a variety of its genera on the genus level. *Escherichia coli* is a Gram-negative, facultative anaerobic, rod-shaped, coliform bacterium of the genus *Escherichia* that is commonly found in the lower intestine of warm-blooded organisms. It was the most prevalent taxa that was reported in 24 articles. In 15 studies, the growth effect of it was shown in CRC patients; on the other hand, in 5 articles, it had decreased presence. *Pseudomonas* is the second common genus of bacteria that can create infections in the body under certain circumstances. Moreover, in this genus, the articles conveyed that the *Caulobacter* were significantly less present in CRC patients. In conclusion, we can see that in most studies, Proteobacteria were present to a greater degree in CRC patients relative to the controls.

5.1 Tumor Sample

5.1.1 Relative Abundance

Analysis of four cases and four controls at the phylum level showed that Proteobacteria members were more abundant in CRC cases (12.9%) compared with controls (4.85%; P<0.05) (32). The data of a study showed the relative abundance of Proteobacteria was 19.65% in a probiotic group, 1.55% in a perioperative placebo group, and 19.65% in healthy volunteers (P>0.001) (37). In another study, at the phylum level Proteobacteria was the most predominant phylum after Firmicutes and Bacteroidetes, contributing to 10.66 and 35.98% of the gut microbiota in cancerous tissues and adjacent non-cancerous tissues, respectively (36). In a research, the second most dominant phylum in colorectal adenoma patients was Proteobacteria (30.1%), but there was a clearly lower relative abundance of this phylum in the NG (3.3%) (34). In Gao's study, at the phylum level, the relative abundance of Proteobacteria was 14.54% in tumor samples vs. 2.74% in adjacent NTs (P>0.05) (40). In another study, the relative abundance of Proteobacteria was 13.34% in a cancer group, 39.92% in AG, and 31.19% in NG (11).

5.1.2 Mean Abundance

The mean abundance of Proteobacteria in a cohort study was 2.9±4.5 in adjacent tumor samples vs. 2.4±2.9 in tumor samples in the US and 3.2±8.9 in adjacent tumor samples vs. 1.7±2.6 in tumor samples in Spain (27). In another study, the mean abundance of Proteobacteria was 2.77 in the NG and 2.92 in the CRC group (P=0.18) (31).

5.1.3 Enrichment

In a study, Proteobacteria were less abundant in the gut microbiota of cancerous tissues than that of adjacent non-cancerous tissues, and the difference was statistically significant (P<0.01) (36).

5.2 Stool Sample

5.2.1 Relative Abundance

Among all bacterial groups revealed by the interpretable sequences, the relative abundance of Proteobacteria contributed to 4.68 and 2.81% of the gut microbiota in CRC patients and NG individuals, respectively (46). One of the three dominant phyla among CRC cases was Proteobacteria, with a presence of 14.51% in cancerous tissues vs. 5.57% in the intestinal lumen (P=0.001) (38). In another research, by analyzing stool samples, the relative abundance of Proteobacteria obtained in CRC was 9.5% vs. 6.8% in the control (P<0.05) (29).

5.2.2 Mean Abundance

The mean abundance rates of Proteobacteria in a cohort study was 5.59E-0 (CRC vs. neoplasia-free) and 8.64E-02 (CRC vs. adenoma) (55).

5.2.3 Enrichment

In Wu's study for Proteobacteria, no significant differences were observed between the NG controls and the CRC patients (20). Participants of another

study were selected from a cohort of 648 patients who were recruited with informed consent between 2004 and 2006 from different endoscopy departments. In this study, Proteobacteria significantly increased in CRC patients (55). In another cohort study, the population under study showed an increase in Proteobacteria in CRC patients (53).

Proteobacteria load is suggested as a potential diagnostic criterion for unstable microbial community (dysbiosis) and diseases. Based on the current study, we propose that an increased or decreased prevalence of the Proteobacteria bacterial phylum is a marker for unstable dysbiosis. Nevertheless, future studies may reveal its exact effects on CRC.

Conclusion

Throughout the past decade, extensive research has been published to identity cancer-related microbiota, especially in CRC where the tumor is located in situ along with the gut microbiota. In addition, current screening tests in CRC have not been translated efficiently in early detection strategies. There is a growing need for developing non-invasive, targeted, and precise screening assays, especially for non-advanced CRC. Gut microbiota is a major component of the intestinal luminal environment and plays an important role in CRC; however, validating microbiota profiles across different populations is out of the way.

There are vast amounts of taxa mentioned in the literature. Some of them are more prevalent, and most articles having demonstrated the presence of Fusobacteria, Firmicutes, Bacteroides, and Proteobacteria in the gut. Furthermore, in most articles, these taxa were more prominent in CRC patients. Conversely, we found that some family, genus, species, and classes of microbiota were less present in CRC patients relative to controls, though some showed non-significant results. In addition, rare taxa were defined as those reported in less than two articles. They were collected in these papers because we wanted to introduce them as a kind of microbiota that can be investigated in future sequencing.

To date, the identification of the best biomarker in terms of affordability and convenience for screening CRC has been out of reach. To overcome this problem, we will require a multicenter study in different ethnic groups of patients to derive the best diagnostic algorithm across populations. Moreover, if we find an accurate profile, it will necessitate concerted efforts from researchers and clinicians to translate it into a clinical product. Furthermore, there is a need for microbial viability and clinical studies to determine the stability and utility of the microbiota, as well as the development of a regulatory framework to govern their use as part of cancer therapy or prevention. One of the most important and challenging issues for determining an accurate microbiota profile is the vast amount of confounding factors like nutrition, ethnicity, physical activity, smoking consumption, and genetics, which could also be responsible for inducing CRC.

In addition, some microbiota like Fn had antagonistic effects on probiotics and were involved in the establishment of the multispecies microbial community in the large intestine; therefore, we should consider the effect of microbial ratio and interactions with probiotics, which could be valuable for prospective epidemiological surveillance and large-scale screening of early CRC.

With these challenging perspectives, there are several directions for research and development regarding microbiota modulation in screening CRC. Firstly, for identifying accurate profiles, we need large cohort studies that provide the opportunity for the researcher to determine valid profiles in general populations. Most of the current studies were done on CRC patients and their controls. As we know, a lot of factors may change the microbiota profile after promoting disease. Secondly, most studies were done on tumor tissues or mucosa. If we want to establish an accurate profile that helps us screen CRC through a non-invasive method, we need fecal samples. Not only should this method be easy but also it should be cost-effective and safe. Therefore, future studies should focus on recognizing and establishing precise microbiota profiles based on fecal samples. Until now, the methods for recognizing microbiota profiles are expensive and not easily accessible in less developing countries. If we want to establish accurate profiles that are accessible for every country, we should first attempt to find new and cost-effective methods for conducting such experiments in various countries with diverse cultures, customs, nutritional, and socio-economic statuses, which are sure to have paramount effects on the promotion of CRC. By and large, although so many studies have been done until now and lots of money has been spent for this area, there is a long journey ahead before microbiota can become an important component of cancer screening. Multi-center cohort studies with the same protocols and similar methods for collecting data and recognizing microbiota profiles will be necessary to achieve our goals.

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Table I: the effect of several taxon on colorectal cancer which showed increase, decrease, unknown or non- significant results

Phylum	Family[	Genus	Species	Class	Total nuber	In-crease	De-crease	Non- sig-nificant	Un-knonw
Actinobacteria									
	Propionibacterium				6	1	4		1
		Collinsella			4		3		1
		Rhodococcus			3	1	1	1	
		Slackia			3		2		1
		Eggerthella			4	2	1	1	
		Microbacterium			2		2		
		Bifidobacterium			10		5	4	1
		Actinomyces			5	4		1	
		Micrococcus			3		3		
		Atopobium			3	2		1	
Acidobacteria					3	1		1	1
Abiotrophia		Granulicatella			8	5	1		2
Bacteroides									
	Prevotella				17	11	4		2
	Enterotoxigenic Bacteroides fragilis (ETBF)				3	3			
		Butyricimonas			3	2			1
		Porphyromonada-ceae			3	3			
		Pedobacter			4		4		
		B. vulgates			1	1			
		Alistipes			7	4	3		
			Flavobacte-riaceae		5		3		2
			Porphyromo-nas		9	8		1	
Cyanobacteria					3	2	1		
Fusobacteria									
	Leptotrichiaceae				3	2			1
		Leptotrichia			3	3			
		fusobacterium			9	9			
Firmicutes									
	Veillonellaceae				4	1	2		1
	Synergistetes				4	1		2	1
	Eubacteriaceae				3	3			
	Lachnospiraceae				12	5	4	1	2
	Oscillospira				4	4			
	Peptostreptococcus				17	14	1		3
		Bilophila			3	2			1
		Turicibacter			3	1			2
		Anaerotruncus			3	1	2		
		Lactococcus			3	2	1		
		Holdemania			3	1	1	1	
		Brochothrix			3		3		
		Anaerostipes			5	4			1
		Pseudobutyrivibrio			3		1	(1	1
		Leuconostoc			4	1		2	1
		Phascolarctobac-terium			7	5	1	1	
		Megamonas			5		5		

		Coprococcus			8	1	4	1	3
		Selenomonas			6	4			2
		Gemella			6	5			1
		Subdoligranulum			6	2	3		1
		Roseburia			14	3	7	2	2
		Ruminococcus			16	8	8		
		Eubacterium			8	3	5		
		Dorea			11	3	5	1	2
		Streptococcus			14	11	2		1
		Butyricicoccus			3	1	1		1
		Bacillus			6	3	3		
		Mogibacterium			2	1	1		
		Parvimonas			11	8	2		1
		Faecalibacterium			12	3	7	2	
		Dialister			8	2	4		2
		Clostridium			14	8	2	3	1
		Staphylococcus			6	3	3		
		Lactobacillus			10	2	3	3	2
			Enterococcus		6	3	2	1	
			Blautia		11	3	7		1
				Clostridiales Pseudoflavonifractor	2	2			
Proteobacteria									
	Bradyrhizobiaceae				3		2		1
	Burkholderiaceae				4	1	2		1
	Enterobacteriaceae				6	5	1		
		Acinetobacter			3		3		
		Leptothrix			3	1	2		
		Comamonas			3	2	1		
		parasutterella			3	1	2		
		Psychrobacter			2	1	1		
		Janthinobacterium			3		2		1
		Brevundimonas			3		3		
		Odoribacter			3	1	2		
		Enhydrobacter			4	3	1		
		Rahnella			2		2		
		Sutterella			5	2	2		1
		Stenotrophomonas			2				2
		Burkholderia			4		3		1
		Bilophila			4	2			2[#]
		Ralstonia			4		1	1	2
		Shigella			3	3			
		Heamophilus			5	3	2		
		Campylobacter			5	4			1
		Klebsiella pneumoniae			2	1	1		
		Pseudomonas			13	8	4		1
		sphingomonas			7	1	6		
		Desulfovibrio			5	4	1		
			E. coli		19	14	3	2	
			Caulobacter		3		3		

		Paracoccus denitrificans		3	1	2	
		Klebsiella pneumoniae		2		2	
			Gamma-proteobacteria	2	1	1	
Tenericutes				3	1	1	1

	*Allali Study performed a comparision between US population and Spanish population)6)	** Nakatsu studyperformed a comparision between adenoma vs adjacent-adenoma, carcinoma and adjacent carcinoma(8)	#Chen Wstudy performed a comparision between tissue sample and stool sample(23)	##Gao Zstudy performed a comparision between tissue sample and stool sample (9)	***Yoon H Comparisons of gut microbiota among healthy control, patients with conventional adenoma, sessile serrated adenoma, and colorectal Cancer
Propionibacterium	In US population: 0.1 ±0.2, in SPAIN population 0.02 ± 0.09 (p value 0.0452)				
Collinsella	In us population 0.1 ±0.1 , in spain population 1.27 ± 1.83 (p value 0.0001)	Normal control(5.1616092) , adenoma(2.946877246) vs. adenoma-adjacent(-1.938527642) , carcinoma(4.54364622) vs. carcinoma-adjacent(-1.952516685)			
Slackia	In us population 0.008 ± 0.02, in spain population 0.05 ± 0.13(p value 0.0426)				
Eggerthella		normal control(0.458208453), adenoma(-0.642759786) vs adenoma-adjacent(-0.457731638) , carcinoma(0.947111682) vs. carcinoma-adjacent(0.277062811)			
Granulicatella			In cancerous tissue 1.63 , in stool sample 0.045 , p value <0.001		
Prevotella		In normal control(-0.963197945) , adenoma (-0.532759147) vs. adenoma-adjacent (3.626384504) , carcinoma (-0.763385754) vs. carcinoma-adjacent(-0.803068649)	In cancerous tissue 6.11 , in stool sample 0.88 , p value 0.011	In cancerous tissue 6.11 , in stool sample 0.88 , p value 0.011	
Enterotoxigenic Bacteroides fragilis (ETBF)		In normal control(2.285773604) , adenoma(0.031463428) vs. adenoma-adjacent(1.172320388) , carcinoma (2.804238773) vs. carcinoma-adjacent (-1.886271168)			
Butyricimonas	In US population 0.06 0.15 , in SPAIN population 0.16 ± 0.25 with p value 0.0054				
Pedobacter		In normal control (1.223773833), adenoma (0.386299122) vs. adenoma-adjacent(-2.852151179), carcinoma(3.04892324) vs carcinoma-adjacent(-2.128952135)			

Alistipes		In normal control (-0.050560244) , adenoma (3.022344646) vs adenoma-adjacent(2.353873987) , carcinoma(0.918112098) vs carcinoma-adjacent(2.544579487)		
Bifidobacterium	In US population 0.0 ±0.0 , in spain population 0.03 ± 0.14 , p value 0.0059			
Flavobacteriaceae			In cancerous tissue 0.196,in stool o. p value is <0.001	In cancerous tissue 0.196, in stool sample 0 , p value <0.001
Leptotrichiaceae	In US population 0.3 ± 0.6 , in spain population 0.0 ±0.0 , p value 0.0194	In normal control (1.101248287) , adenoma(3.131775716) vs. adenoma-adjacent (-0.482681179) , carcinoma (5.609163916) vs carcinoma-adjacent(-1.587239112)	In cancerous tissue 2.87, in stool 0.68, p value is 0.041	
Veillonellaceae			In cancerous tissue 0.142, in stool sample 0. P value is 0.002	
Synergistetes			In cancerous tissue 0.142, in stool sample 0. P value is 0.002	
Lachnospiraceae	In US population 1.93 2.37 , in spain population 4.65 ± 5.44 p value is 0.0328	In normal control(1.323353266), adenoma (-1.749451693) vs. adenoma-adjacent(0.788219201), carcinoma(-0.038581465) vs. carcinoma-adjacent(0.112509951)	In cancerous tissue 17.11, in stool sample 46.66, value is <0.001	
Oscillospira		In normal control(1.04321151), adenoma(0.384973076) vs adenoma-adjacent(1.973650464) , carcinoma (-0.102447942) vs. carcinoma-adjacent(3.040352433)		
Peptostreptococcus		In normal control(4.612349478) , adenoma(-0.099315404) vs. adenoma-adjacent(6.653273185), carcinoma(8.148466047) vs carcinoma-adjacent(1.044333722)	In cancerous tissue3.39 in stool sample0.29 p value is <0.001	In cancerous tissue 3.39, in stool sample 0.29 , p value <0.001
Bilophila	In US population 0.0 0.0 and in spain population 0.02±0.04 p value 0.0014			
Turicibacter	In US population 0.0 ± 0.0 and in spain population 0.02 § 0.09 p value 0.0118		In cancerous tissue 0.005 , in stool sample 0.145. p value is 0.008	
Anaerostipes	In US population 0.0 § 0.0 , in spain			
Pseudobutyrivibrio			In cancerous tissue 1.77 , in stool sample 7.74 , p value is 0.004	
Coprococcus	In US population 0.09 § 0.12 , In Spanish population 1.41 § 2.58 , p value is 0.0002	In normal control(0.71277227), in adenoma(-1.615245009) vs adenoma-adjacent(5.076187666), carcinoma(0.858556039) vs carcinoma-adjacent(-0.532428331)	In cancerous tissue 0.90 , in stool sample 1.50 , p value is 0.025	

Selenomonas	In US population 0.09 § 0.12 , In Spanish population 1.41 § 2.58 , p value is 0.0002 in US population0.6 § 1.9 , in Spanish population 0.0 § 0.0 , p value is 0.0037		In cancerous tissue 0.24, in stool sample 0 , p value 0.002		
Gemella	significantly over represented in Spanish tumors	In normal control (2.585796071) , adenoma(0.709235201) vs adenoma-adjacent(3.227887372) , carcinoma(1.604643747) vs carcinoma-adjacent(-1.365886379)	In cancerous tissue1.97, in stool sample 0.65, p value <0.001		
Subdoligranulum		In normal control (-0.203228369) , in adenoma(0.544701678) vs adenoma-adjacent(-0.734580522) , carcinoma(1.390323695) vs carcinoma-adjacent(0.444504302)			In Sessile Serrated Adenoma patient
Roseburia			In cancerous tissue 0.23 , in stool sample 2.08 , p value <0.001	In cancerous tissue 0.23 , in stool sample 2.08. p value is <0.001	
Ruminococcus	In Spanish Tumor -adjacent (3.56 § 5.6) vs Tumor (3.16 § 4.92) p value 0.0147				In conventional adenoma, SSA, and colorectal cancer (CRC) groups
Dorea	In US population 0.27 § 0.44 , in Spanish population 1.30 § 1.61, p value 0.0355				In Sessile Serrated Adenoma, and advanced colorectal neoplasm;
Streptococcus	significantly over represented in Spanish tumors	In normal control (4.612349478) , adenoma(-0.099315404) vs adenoma-adjacent(6.653273185) , carcinoma(8.148466047) vs carcinoma-adjacent(1.044333722)	In cancerous tissue 10.19 , in stool sample 2.45 , p value 0.001		
Butyricicoccus		In normal control (0.351123169) , adenoma(-0.344320509) vs adenoma-adjacent(1.74736073) , carcinoma(2.259607869) vs carcinoma-adjacent(0.952362114)			
Mogibacterium		In normal control(0.29031597) , adenoma(3.039014842) vs adenoma-adjacent(-0.00823166) , carcinoma(-0.577663838) vs carcinoma-adjacent(0.465635953)			
Parvimonas	significantly over represented in Spanish tumors	In normal control(5.961165432) , adenoma(-0.052002654) vs adenoma-adjacent(5.710793656) , carcinoma(8.583456578) vs carcinoma-adjacent(2.147148475)			

Faecalibacterium		In normal control (0.627665212) , adenoma (2.321669214) vs adenoma-adjacent (3.149185714) , carcinoma(0.791260906) vs carcinoma-adjacent(0.056496993)		
Dialister			In cancerous tissue 0.49 and in stool sample 0.086 . p value is 0.014	
Clostridium		In normal control(1.314422284) , adenoma (3.37487887) vs adenoma-adjacent(0.130245064) , carcinoma (1.159752361) vs carcinoma-adjacent(-0.313733318)	In cancerous tissue 0.128 , stool sample 0.300 , p value 0.033	Increased in sessile serrated adenoma;
Lactobacillus	In US population 0.03 § 0.13 , in Spanish population 0.43 § 1.00 , p value 0.0143		In cancerous tissue 0.022 in stool sample 2.88 ,p value0.009	
Blautia			In cancerous tissue 0.61 , in stool sample 3.70, p value <0.001	In normal control (3.459510257) , adenoma (0.809369078) vs adenoma-adjacent (3.032727148) , carcinoma (1.736505429) vs carcinoma-adjacent(0.488957412)
Bradyrhizobiaceae	In US population 0.0 § 0.0 , in Spanish population 0.16 § 0.77, p value 0.0454			
Burkholderiaceae			In cancerous 0.64 , in stool sample 0, p value 0.001	
Enterobacteriaceae		In normal control (3.171562831) , adenoma (-1.022284411) vs adenoma-adjacent (-1.65760431) , carcinoma (0.112888902) vs carcinoma-adjacent(-0.328006255)		
Odoribacter		In normal control (0.148191703) in adenoma (1.675973017) vs adenoma-adjacent (0.473504183) , carcinoma(1.212604045) vs carcinoma-adjacent(1.333243557)		
Sutterella		In normal control (2.502479582) , adenoma (0.688452833) vs adenoma-adjacent(1.700547208) , carcinoma(0.93962918) vs carcinoma-adjacent(-1.964318227)	In cancerous tissue 0.42 , in stool sample 0.17. p value is 0.034	
Stenotrophomonas	population 0.0 In US § 0.0 , in spain population 0.007 § 0.01 . p value 0.0454		In cancerous tissue 0.188 , in stool sample 0.001 .p value is 0.023	
Burkholderia			In cancerous tissue 0.067 , in stool sample 0, p value 0.007	

Bilophila	In US population 0.03 § 0.15 , in Spanish population 0.03 § 0.05 , p value 0.0101		In cancerous tissue 0.14 , in stool sample 0.04 , p value 0.001	
Ralstonia	In US population 2.1 § 4.2 , in Spanish population 0.9 § 4.3, p value is <.0001		In cancerous tissue 0.55 ,in stool sample o. p value is 0.023	
Campylobacter	In us population 0.5 § 2.0 , in spain population 0.0 § 0.0 , p value 0.0122			
Pseudomonas		In normal control (-1.247341769) , adenoma(-4.693182574) vs adenoma-adjacent (7.035175515) , carcinoma(7.395705169) vs carcinoma-adjacent (0.017546965)	In cancerous tissue 0.53, in stool sample 0 , p value 0.001	
sphingomonas				In Sessile Serrated Adenoma, and advanced colorectal neoplasm;
E. coli		In normal control (4.720815833) , adenoma(-3.975448755) vs adenoma-adjacent (-0.853693675) , carcinoma(7.596182202) vs carcinoma-adjacent(-0.427038241)		

Supplementary I: The characteristics of articles which were included in the study

	Author, Year	Country	Method	Type of study group	Age	Sex	Sample Size	Stage	Type of study	Type of specimen	Type of process
1	Kehan Xu, 2017	China	Sequencing	Normal/ Adenoma/ cancer	Normal: 60.13±5.99 Adenoma: 67.32±8.80 Cancer: 67.85±13.18	UN	160	various stage	Case control	Mucosa	UN
2	Swidsinski, 1998	Austria	Sequencing	Asymptomatic controls/ Symptomatic Controls/ Adenoma/ Carcinoma	Asymptomatic controls: 57.6 Symptomatic Controls: 39.1 Adenoma: 60.9 Carcinoma: 61	female :72 / male :53	94	UN	Case control	Tissues	Frozen
3	Li, 2016	China	Sequencing	CRC/ non-cancerous tissues	51.5% age below 65/ 48% age upper 65	Male :55 / female;46	101	UN	Case control	Tissues	Embedded in paraffin
4	Zhou, 2016	China	Sequencing	Tumor tissue / Adjacent normal tissue	64.5773 ± 1.1973	Male : 61 / female; 36	97	I,II,III,IV	Case control	Tissues	Frozen
5	Ohigashi, 2013	Japan	Sequencing	colorectal cancer/ adenoma 6group / non-adenoma group	CRC: 68.9 ± 12.1/ Adenoma :66.6 ± 9.2/ Non-adenoma: 65.6 ± 13.5	Male : 76 / female; 66	142	I,II,III,IV	Case control	Stool	Fresh
6	Yan, 2017	China	Sequencing	Tumor / adjacent normal tissues	Unknown	Male : 158 / female; 122	280	III/IV	Case control	Tissues	Embedded in paraffin
7	Alomair, 2018	Saudi Arabia	Sequencing	CRC/healthy control	age range: 38–77	Male : 15 / female; 14	29	I, II, and III	Case control	Mucosa	Frozen
8	kASAI, 2016	Japan	Sequencing	Control/ Adenoma/ Cancer	Control: 48.8±8.2 / Adenoma: 53.5±9.3 / Cancer: 54.3±7.9	Male: 53 / female; 55	108	early-stage	Case control	Stool	suspended in a solution

9	Yoon, 2017	Korea	Sequencing	Control/ advanced colorectal neoplasm/ advanced colorectal neoplasm/ colorectal cancer	mean age: 61.75 ± 10.86	UN	24	I, IIA, IIIB, IIIC, IV	Case control	Tissues	Fresh
10	L Warren, 2013	Canada	Sequencing/ culture	Control/ Tumor	UN	UN	130	UN	Case control	Tissues	Frozen
11	Huang,2018	UN	Sequencing	CRC/ control	Case 40-55: 30.76% 55-70:30.76% 70-85: 38.47% Control: 40-55: 16.70% 55-70:25.00% 70-85:58.30%	Male: 22 / female; 29	55	I, IIA	Case control	Tissues	UN
12	Li, 2015	China	Culture	CRC/ control	UN	UN	40	UN	Case control	Stool	Frozen
13	Geng, 2013	China	Sequencing	CRC/ control	22.97±1.56	Male:8 Female:8	16	UN	Case control	Tissues	Frozen
14	Wu, 2013	USA	Sequencing	CRC/ control	CRC: 58.3± 8.7 Control: 53.2±5.4	Male:21 Female:18	39	UN	Case control	Stool	Frozen
15	Magdy, 2015	Egypt	Culture	CRC/ control	CRC: 50.43 ± 8.13 (34-69) Control: 49.64 ± 9.9 (24-68)	Male:278 Female:183	461	UN	Case control	Mucosa	Fresh
16	Kohoutova 2014	UK	Culture	CRC/CRA/ control	CRA: aged 39–79, mean age 63 ± 9 CRC: aged 38–86, mean age 67 ± 11 Control: age 23–84, mean age 55 ± 15	Male:49 Female:31	80	Stage I,II, III IV	Case control	Mucosa	Frozen
17	Liang, 2017	China	Sequencing	CRC/ control	CRC: mean age, 67.2 ± 11.6 years Control: 59.3 ± 5.8 years	Male:177 Female:193	439	Stage I,II, III IV	cohort	Stool	Frozen
18	J. Goedert, 2015	USA	Sequencing	CRC/CRA/ other condition	Median : 65 (61–69)	Male:28 Female: 40	68	UN	Case control	Stool	Frozen
19	Sinha, 2016	USA	Sequencing	CRC/ control	CRC: 63.4 ±13.1 Control: 58.4 ±13.0	Male:81 Female: 40	131	Non-invasive /Invasive, no known metastases /Metastatic /	Case control	Stool	Frozen
20	L.Amitay, 2017	Germany	Sequencing	CRC/Advanced adenoma/ Non advanced adenoma/ control	CRC: 66.9 Advanced adenoma: 64.8 Non advanced adenoma: 62.4 Control: 62.1	Male:280 Female:220	500	Stage I,II, III IV	Case control	Stool	Frozen
21	Tahara, 2014	USA	Sequencing	CRC/ control	CIMP negative: 64.0 ±1.9 CIMP1: 71.8 ± 1.3 CIMP2 : 66.7 ± 1.6	Female: 60	310	UN	Case control	Tissue	UN
22	N. McCoy, 2013	USA	Sequencing	CRC/ control	CRC: 56.3± 60.92 Control: 55.90±0.88	UN	115	T-2/ T-3	Case control	Tissue	Paraffin embedded
23	Flanagan, 2014	Czech Republic	Sequencing	CRC/CRA	CRC/CZ: 70±10 CRC/DE: 67±11 CRC/IE: 61±11 CRA: 63±8	Male:108 Female:66	174	UN	Case control	Tissue	Frozen

24	Sun,2016	China	Sequencing	CRC/ control	median age of 62 years (range, 28–84 years)	Male:95 Female:57	152	Stage I,II, III IV	Case control	Tissue	Frozen
25	Castellarin, 2012	Canada	Sequencing	CRC/ control	UN	UN	99	Early stage	Case control	Tissue	Fresh
26	WANG, 2017	China	Sequencing	CRC/ control	average age of the patients was 52.5 years (range, 40-60 years)	Male:9 Female:6	27	Stage II, III IV	Case control	stool	Frozen
27	Allali, 2015	USA	Sequencing	Tumor/ tumor adjacent	mean age and range of US matched tumor and adjacent tissues were 63.6 and 42–88	Male:26 Female:19	45	UN	cohort	Tissue	Frozen
28	Feng, 2015	China	Sequencing	Control / advanced adenoma/ carcinoma	45–86	Male:64 Female:64	147	Stage II, III	Case control	stool	Frozen
29	Allali, 2018	Morocco	Sequencing	CRC/ control	CRC: 52.8± 54 Control: 49.3± 46	Male:5 Female:18	23	UN	Case control	stool	Frozen
30	Nakatsu, 2015	China	Sequencing	Normal control / Adenoma-adjacent /Adenoma Carcinoma-adjacent /Carcinoma	50–70 years	UN	160	Stage II, III IV	Case control	Mucosa	Frozen
31	Chen, 2012	Italy	Sequencing	CRC/ control	Healthy Volunteers swab: 56(42–77) Healthy Volunteers stool: 64(37–84) CRC Volunteers swab: 65(37–86) CRC Volunteers stool: 64(37–78) CRC Volunteers tissue: 61(37–81)	Male: 77 Female: 59	136	UN	Case control	Swab/ stool/ tissue	Frozen
32	Sanapareddy, 2012	USA	Sequencing	CRC/ control	Case: 57.45 (1.11) Control: 55.70 (1.08)	Male: 39 Female:32	71	UN	Case control	Mucosa	Frozen
33	Yu, 2017	Denmark	Sequencing	CRC/ control	CRC: median age 67 Control: median age 62 years	Male:81 Female:47	128	Stage I,II, III IV	Nested case control	stool	Frozen
34	Mira-Pascual, 2015	Japan	Sequencing	CRC/ polyp/ control	CRC: 71.1 ± 10.1 Polyp: 63.3 ± 13.1 Healthy: 52.6 ± 15.2	Male:18 Female:10	28	UN	case control	Stool tissue	Frozen
35	Gao, 2015	China	Sequencing	CRC/ control	CRC: 67 ± 7.2 Healthy: 70 ± 5.1	Male:29 Female:32	61	Stage (A/B/C)†	case control	Mucosa/ Tissue	Frozen
36	M. Dejea, 2014	USA	Sequencing	CRC/ control	UN	UN	36	UN	Case control	Mucosa	UN
37	Gao,2017	China	Sequencing	CRC/ control	Male: 63.89 Female: 63.08	Male: 35 Female: 30	65	Stage I,II, III IV	Case control	Mucosa	Frozen
38	Lu, 2016	China	Sequencing	CRC/ control	CRC: 53.95±6.1 Control: 52.95±5.3	Male:21 Female: 30	51	Various stage	Case control	Tissue	Frozen
39	Mahmoudvand, 2017	Iran	Sequencing	CRC/ control	Mean age:54	Male:112 Female: 98	200	UN	Case control	Tissue/ Mucosa	Frozen
40	Zeller, 2014	Germany, France, Japan	Sequencing	CRC/ Adenoma/ Control	UN	UN	335	Stage 0, I,II, III IV	Case control	Stool	Frozen

41	GAO, 2015	China	Sequencing	CRC/ Control	40-75	Male:18 Female:15	33	A/B/C	Case control	Tissue/ Mucosa	Frozen
42	Wong, 2017	China	Sequencing	CRC/ advanced adenoma / Control	Mean age: 61.8	Male:200 Female:109	309	Stage I,II, III IV	Case control	Stool	Frozen
43	Balamurugan, 2008	India	Sequencing	CRC/ Control	colorectal cancer : ranged in age from 18 to 77 years (median 51.5 years)/ upper gastrointestinal cancer: ranged in age from 40 to 67 years (median age 54 years) Healthy volunteers: ranged in age from 18 to 60 years (median 39 years)	Male:31 Female:15	46	UN	Case control	Stool	Frozen
44	L. Weir, 2013	USA	Sequencing	CRC/ Control	Mean :43.4	Male:11 Female:10	21	T1,T2,T3	Case control	Stool	Frozen
45	Chirouze,2013	France	Sequencing	Normal colonoscopy/ Non-tumoral lesions/ Adenoma/ Carcinoma	mean age 59.5 years, range 22–90	UN	27	UN	Case control	Stool	Frozen
46	Andres-Franch,2017	Spain	Sequencing	Normal/Tumoral	Median age 70 (range: 30–94) years	Male: 95 Female:95	190	II, III	cohort	Tissue/ Mucosa	Frozen
47	Wang, 2012	China	Sequencing	CRC/ Control	Healthy volunteers Age (median, range): 49, 40–54 CRC patients Age (median, range): 60, 42–77	Male:51 Female:51	102	Stage I,II, III IV	Case control	Stool	Frozen
48	Ai,2017	China	Sequencing	normal, CRA / CRC	Population A Control : 52.29 ± 1.53 CRA : 58.89 ± 1.48 CRC: 62.88 ± 1.50 Population B Control : 60.57 ± 1.46 CRA : 60.30 ± 1.67 CRC: 66.81 ± 1.494	Male:138 Female:144	282	Stage I,II, III IV	Case control	Stool	Frozen
49	P. Zackular, 2014	USA	Sequencing	Healthy/ Adenoma/ Cancer	Healthy: 55.3 (9.2) Adenoma: 55.3 (9.2) Cancer: 55.3 (9.2)	Male:50 Female:40	90	Early stage	Case control	Stool	Frozen
50	Flemer, 2017	ireland	Sequencing	Cotrol/Polyp/ CRC	Tissue Control: 53.2±13.5 Stool Control: 63.9±11.1 Stool CRC: 65.3±10.8 Swab Control: 51.5±12.4 Swab CRC: 65.7±10.9 Swab Polyp: 59.2±15.1	UN	234	UN	Case control	STOOL/ Swab/ Tissue	Fresh
51	WACHS-MANNOVA, 2018	Slovakia	Culture	CRC/Adenoma /Control	Healthy : median :62 28-82 Adenoma: median :59 36-72 Carcinoma: 68 57-79	Male:11 Female:18	29	UN	Case control	Tissue	Fresh

52	M. Thomas	Brazil	Sequencing	Rectal/Control	Healthy: 55.2 ± 15.7 Rectal : 59.3 ± 8.8	Male:19 Female:17	36	pT1, pT2	Case control	Tissue	Fresh
53	R. Marchesi, 2011	India	Sequencing	colon tumor tissue/ adjacent non-malignant mucosa	Mean 63.5	Male:5 Female:1	6	T2,T3,T4	Case control	Tissue	Frozen
54	Sobhani, 2011	France	Sequencing	CRC/ control	CRC:mean: 67.1±11.6 Normal: 55.8±11.6	Male:86 Female:93	179	stage I or II	case control	stool	Frozen

Supplementary II: The following microbiom are rare taxon which was reported only in one or two articles

A. finegoldii Achromobacter Acidovorax Acidocella Acidomonas Adhaeribacter aquaticus Adlercreutzia Aerococcaceae Aeromonadales Agrobacterium AlcaligenaceaeAlcaligenes Alkaliphilus Allisonella Alloprevotella Alphaproteobacteria Anoxybacillus Anaerobacter Anaerococcus Anaerosporobacter Anaerospites Anaerovorax Arthrobacter Asinibacterium Bacilli Barnesiella Beggiatoa sp. PS Betaproteobacteria Bradyrhizobium Brevibacterium B. massiliensis Burkholderiales Buttiauxella Butyrivibrio Bulleidia Catonella Campylobacteracea C. coccoides C. leptum Carnobacteriaceae Carnobacterium Catenibacterium Chitinophaga Chlorobiaceae Chloroflexi Chlorobacteria Chryseobacterium Clostridiales bacterium 1_7_47FAA Clostridiaceae Clostridium hathewayi Cetobacterium Comamonadaceae Con 4295 Coprobacillus Coriobacteriaceae Corynebacterium Coxiellaceae Crenothrix polyspora Crenotrichaceae Crenarchaeota Cryocola Cupriavidus Cynobacteria Cyanobacterium (10)Deinococci Delftia Deltaproteobacteria Dermabacter Desulfovibrionales Dehalobacterium Devosia E.faecalis Elkenella Eikenella Enterobacteriales Enterorhabdus Epilithonimonas Epsilonproteobacteria Erysipelotrichidae Erythrobacteraceae Erysipelotrichaceae Exiguobacterium Euryarchaeota Epulopiscium Enterococcaceae Fastidiosipila F. prausnitzii Faecalibacterium prausnitzii f_Christensenellaceae f_Dehalobacteriaceae
Filifactor Filifactor alocis Flavimonas Flavobacterium Geobacillus Gemmiger Gordonia Gordonibacter Haladaptatus Halomonas Howardella Hungatella Hypersegal Jeotgalicoccus Johnsonella lautropia Lawsonia Leuconostocaceae Lentisphaerae Limnohabitans Lysinibacillus Malassezia globose Massilia Mesorhizobium Methanosphaera Methylobacterium Methylobacteriaceae Mogibacteriaceae Moraxellaceae Morganella Moryella Mucispirillum Mycobacteriaceae Mycobacterium
Mycoplasmataceae Myroides Neisseriaceae Neisseriales Nesterenkonia Nevskia Nitriliruptor Novosphingobium Oceanobacillus Ochrobactrum Olsenella Oxalobacteraceae Oribacterium Oscillibacter Oxalobacter Paraprevotella Paenibacillus Pasteurellaceae Pasteurellales Pediococcus Peptoniphilus indolicus Phyllobacterium Proteus vulgaris Pseudomonadales Pseudomonas aeruginosa Pseudomonas veronii Pseudoxanthomonas P. merdae Renibacterium Rhodanobacter Rhodobacteraceae Rhodoferax ferrireducens Rhodocyclaceae Rhodospirillales Rothia Rubrobacter Ruminiclostridium Salinispora Sarpulinacea Shewanella Shewanellaceae Schwartzia Solibacillus Solobacterium Solobacterium moorei Sphingobacteria Sphingopyxis Sphingobium SMB53 Sporosarcina Streptobacillus moniliformis Streptophyta Syntrophomonadaceae Tenerecuites Tepidimonas Thalassospira Thiotrichaceae Trabulsiella Verrucomicrobiaceae Victivallis Weissella Xanthomonadales Xanthomonas