Artículo de Revisión Sistemática / Systematic Review Article

Gut microbiota in colorectal cancer: Evidence from observational studies

Microbiota intestinal en el cáncer colorrectal: Evidencia de estudios observacionales

ABSTRACT

*This study proposes to update knowledge about the relationship between microbiota and Colorectal Cancer (CRC). This is a review carried out using the methodology of the Preferred Report Item for Systematic Analysis and Meta-Analysis (PRISMA) and search for original articles, indexed in the Pubmed, Cochrane and Science Direct databases, published between 2011 and 2019, in English. Ten articles showed changes in bacterial composition and its influence on the development and progression of CRC, and only two addressed changes in the composition of fungi and their relationship with CRC. Most studies have shown that the increase in *Fusobacterium nucleatum* and *bacteroides fragilis* is strongly associated with the occurrence of CRC due to inflammatory mechanisms; and that *Faecalibacterium prausnitzii* is a protective factor through the production of butyrate. Additional research is recommended to assess the relationship of microorganisms with the development of CRC, with an emphasis on fungi.*

Keywords: Bacterium; Colon; Dysbiosis; Fungi; Malignant neoplasm; Recto.

RESUMEN

*Este estudio propone actualizar el conocimiento sobre la relación entre la microbiota y el Cáncer Colorrectal (CCR). Esta es una revisión realizada utilizando la metodología del Elemento de Informe Preferido para el Análisis Sistemático y el Meta-análisis (PRISMA) y la búsqueda de artículos originales, indexados en las bases de datos Pubmed, Cochrane y Science Direct, publicados entre 2011 y 2019, en inglés. Diez artículos mostraron cambios en la composición bacteriana y su influencia en el desarrollo y la progresión del CCR, y solo dos abordaron los cambios en la composición de los hongos y su relación con el CCR. La mayoría de los estudios han demostrado que el aumento de *Fusobacterium nucleatum* y *bacteroides fragilis* está fuertemente asociado con la aparición de CCR debido a mecanismos inflamatorios; y que *Faecalibacterium prausnitzii* es un factor protector a través de la producción de butirato. Se recomienda investigación adicional para evaluar la relación de los microorganismos con el desarrollo de CCR, con énfasis en los hongos.*

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Palabras clave: Bacteria; Colon; Disbiosis; Hongos; Neoplasma maligno; Recto.

INTRODUCTION

Intestinal microbiota refers to a set of microorganisms found in the Gastrointestinal Tract (GT), which can establish symbiotic and pathogenic relationships with the host¹. It is known that the bacterial diversity of the colonic environment can be influenced by factors such as type of delivery, breastfeeding, introduction of complementary feeding, environmental contamination, use of antimicrobials, the immune system and genetic characteristics².

In this context, the intestinal environment is the main site of colonization of groups of bacteria that may, depending on

the type, generate or not beneficial effects. *Bifidobacterias* and *Lactobacillus* are described as potentially protective, as they act as barriers to inflammatory events and changes in the colonic environment. In turn, *Enterobacteriaceae* and *Clostridium*, for example, are known to considerably compromise intestinal physiology^{1,3}.

The genus *Bacteroides* is mentioned as the most found in the intestinal microbiota, but it acts as an opportunistic pathogen, represented mainly by the species *Bacteroides fragillis*, which conditions the action of virulence and resistance factors to several antimicrobials and, therefore, can alter the microbiota. In some cases, this same genus can benefit its host, and exclude potentially harmful substances from the intestine, which identifies some controversies in its activity^{3,4}.

Classically, the microbiota performs essential functions for homeostasis, which involves the preservation of immunity, enabling the activation of immune defenses; strengthening of the epithelial barrier; protection against pathogens by competitive exclusion, occupying adherence sites in tissues; participation in the absorption of nutrients and metabolism of complex carbohydrates and proteins^{1,5}.

Therefore, it is recognized that many imbalances in the composition of the microbiota, generally characterized by a significant reduction in beneficial microorganisms and an increase in pathogens, can install pathological conditions, such as intestinal dysbiosis. It is also worth mentioning that the decrease in diversity that makes up the colonic environment can also represent a potential cause for this disharmony. Studies currently report that dysbiosis is strongly associated with the occurrence of several diseases, including colorectal cancer, mainly because it considers the intestinal route a key to the events of inflammation and tumorigenesis (CRC)^{6,7,8}.

CRC, which anatomically compromises the colon and rectum, stands out for being the malignant neoplasm with the highest prevalence rates worldwide, being caused by genetic, metabolic and environmental factors^{7,9,10}.

Studies argue that the involvement of the microbiota in the development of colorectal neoplasms is possibly justified by its promoting effect of the release of potentially carcinogenic compounds, of inflammatory mechanisms, which, consequently, favor the proliferation of specific bacterial populations associated with tumorigenesis^{11,12,13}.

Based on the above, the objective of the present study was to update knowledge about the relationship between microbiota and the development of CRC, with a view to promoting and contributing to the conduct of experimental research that offers strategies to improve the dysbiotic profile in the context of cancer, as well as the prognosis and survival of patients with this neoplasm.

METHODS

This is a critical review study conducted between June and July 2019, using the methodology of the Preferred Report Item for Systematic Reviews and Meta-Analyses

(PRISMA)¹⁴. The research was carried out by two authors (DJMS and LLCS), independently, retrieving publications in English, from the years 2011 to 2019, indexed in Pubmed, Cochrane or Science Direct. Searches were compared and equivalence verified in the selection and analysis of the articles. All disagreements, such as the decision to include or exclude, were identified, discussed and resolved by consensus and/or respecting the decision of the most experienced researcher.

The guiding question of the study was defined as: "What is the influence of colonic composition on the development of colorectal cancer in adults?" and the PECO strategy¹⁵ was used to establish Patients (Adults with CRC), Exposure (CRC), Comparison (Adults without colorectal cancer) and Outcome (Positive association between dysbiosis and CRC). The bibliographic analysis was performed combining the following terms recorded in the DeCS (Health Sciences Descriptors): Dysbiosis, Colorectal Neoplasms, Microbiota, Microbiome.

Eligibility criteria included observational studies, conducted in humans aged ≥ 18 years, of both sexes, which investigated the influence of dysbiosis on the development of colorectal cancer. Clinical trials, review articles and experimental studies were excluded. The articles were identified according to time variables and through the application of filters; therefore, the recruited articles were distributed in a spreadsheet to identify duplicates. Initially, the titles and abstracts were read and, finally, the complete reading made it possible to identify the eligibility criteria and define the inclusion or exclusion of scientific materials. Details of the selection are shown in figure 1.

RESULTS

285 articles were identified in PubMed (n= 134), Cochrane (n= 4) and Science Direct (n= 147). After selecting and removing duplicate articles, twelve articles were identified as eligible for this review. The information extracted from the articles to compose the results panel were: authors, year of publication, type and place of study, sample size, objective, methods and main results (Table 1).

Most of the studies analyzed were carried out on the Asian continent, in addition to four in Europe and one in Africa, all with participants of both sexes. Of the twelve articles evaluated, six were cohorts, three were case-control and three were cross-sectional studies. All found a positive association between dysbiosis and CRC. In relation to biological material used for composition analysis bacterial activity, six studies evaluated the fecal samples of the participants^{16,17,18,19,20,21}, four analyzed colorectal tissue biopsies^{22,23,24,25}, one study evaluated biopsy and fecal sample²⁶ and one used secondary data from a hospital system²⁷.

Among the twelve selected studies, ten identified changes in bacterial composition and only two found that changes, mainly in the fungal environment, contributed to the development and progression of CRC.

Figure 1: Study Selection Flow Chart.

Considering initially the data that involved the bacterial composition, 50% (n= 6) of the analyzed studies suggested that individuals with CRC, adenocarcinoma or polyps, are more likely to increase the concentrations of bacteria of the phylum *Fusobacteria*^{16,21,22,,24,25,27} and, specifically, 41.7% (n= 5) of the total, found the prevalence of *Fusobacterium* in the group with CRC, when compared to healthy individuals^{22,24,25,26 27}.

It should also be noted that 25.0% (n= 3) of the findings, found that the risk of CRC was increased due to the bacteremia caused by *B. fragilis* and *F. nucleatum*^{25,26,27}. In addition, *F. nucleatum*, a species belonging to the *Fusobacterium* genus, has been reported to be closely associated with CRC due to its ability to stimulate tumor proliferation through the adhesion gene FadA¹⁶.

Table 1. Summary of relevant aspects of articles included in this review.

Author and Reference	Study Type	Study Location	Objetives	Sample size (n)	Analysis	Outcomes
Coker et al. ¹⁷	Cohort	Hong Kong	Characterize the enteric microbiome of patients with CRC	n= 184 (CRC); 197 (adenoma) n= 204 (healthy)	Analysis of fecal metagenomic sequences	The groups presented significant amounts of phyla <i>Ascomycota</i> and <i>Basidiomycota</i> , but with a greater proportion in patients with CRC
Allali et al. ¹⁶	Cohort	Morocco	Compare stool microbiome between Moroccan CRC patients and healthy individuals	n= 11 (CRC) n= 12 (healthy)	16S rRNA fragment sequencing of stool samples and functional predictive data analysis	Increased <i>B. fragilis</i> and <i>F. nucleatu</i> was found in patients with CRC
Kwong et al. ²⁷	Cohort	Hong Kong	To investigate associations between specific gut bacterial bacteremia and CRC occurrence	n= 13,096 (with bacteremia); n= 32,857 (without bacteremia)	Secondary Data from the Clinical Data Analysis and Reporting System	Specific members of the intestinal microbiota (<i>S. gallolyticus</i> , <i>B. fragilis</i> and <i>F. nucleatum</i>) promoted colorectal carcinogenesis
Gao et al. ¹⁸	Case Control	China	To evaluate the biodiversity, composition and the impacts of the anatomical position and tumor stage on the microbiota	Case= 74 (CRC); 29 (polyps) Control= 28	16S rRNA Gene Sequencing	The <i>Ascomycota</i> : <i>Basidiomycota</i> ratio was shown to be higher in the CRC group compared to the other groups, which indicates fungal dysbiosis
Kinross et al. ²²	Cross-Sectional	United Kingdom	To evaluate the variation of local colonic dysbiosis between tumor and normal mucosa, cancer microbiome and interactions	n= 18 (CRC)	16S rRNA gene sequencing and metabolic analysis	It was observed that the <i>F. nucleatum</i> bacteria was in excess in colorectal tumors. CRC mucosa microbiome is individualized and evolves with disease stage
Wei et al. ²⁵	Cohort	China	Examine microbial structure in CRC tumor samples and assess microbiota correlation	n= 180 (CRC)	16S rRNA Gene Sequencing	It was observed that the greater abundance of <i>Fusobacterium nucleatum</i> and <i>Bacteroides fragilis</i> was associated with a worse prognosis, induced by intestinal inflammation
Nakatsu et al. ²⁴	Cohort	Hong Kong and China	To characterize the microbial communities in the human intestinal mucosa in different phases of CRC	n= 61 (normal colon); n= 47 (adenoma); n= 52 (invasive adenocarcinoma)	16S rRNA Gene Sequencing	It was observed that the metacommunity E represented by the predominance of <i>Fusobacterium</i> and other <i>Firmicutes</i> was strongly associated with colorectal carcinoma
Mira-Pascual et al. ²⁶	Case Control	Spain	Examine the hypothesis that microbiota composition during CRC progression may differ depending on disease stage	n= 7 (CRC); n= 11 (adenomas); n= 10 (normal colon)	16S rRNA gene pyrosequencing, qPCR of specific	Members of the <i>Bacteroides</i> genus have been shown to have high rates of colonization in patients with CRC. In addition, an increase in <i>Enterococcus spp.</i> in the CRC group

...table 1 below.

Author and Reference	Study Type	Study Location	Objetives	Sample size (n)	Analysis	Outcomes
Ohigashi et al. ¹⁹	Cross-Sectional	Japan	To investigate changes in intestinal environments in patients with CRC or adenoma	n= 93 (CRC) n= 49 (healthy)	RT-qPCR Bacterial Count, Fecal Organic Acid Concentration and pH Measurements	The bacterial counts of <i>C. difficile</i> , <i>C. perfringens</i> and <i>Pseudomonas</i> (highly pathogenic) were higher in the CRC group, although not significantly different
Wu et al. ²¹	Case Control	China	Compare microbiota composition of faecal samples from CRC patients and healthy patients	Case= 19 (CRC) Control= 20 (healthy)	Pyrosequencing of the 16S rRNA gene V3 region from faecal samples	A significant increase of several bacterial groups (<i>Bacteroides</i> and <i>Fusobacterium</i>) in the faecal microbiota of the CRC group was observed
Marchesi et al. ²³	Cross-I Sectiona	Netherlands	Provide the first high-resolution map of CRC-associated colonic dysbiosis	n= 6 (undergoing CRC resections)	Bacterial rRNA pyrosequencing	The data showed a general trend of more <i>Bacteroidetes</i> and less <i>Firmicutes</i> in the tumor tissue compared to the adjacent non-tumor mucosa
Sobhani et al. ²⁰	Cohort	France	Analyze the microbiota of healthy patients and those with CRC cancer patients	n= 60 (CRC) n= 119 (normal colonoscopy)	16S rRNA gene pyrosequencing and species quantification by qPCR	A significant increase in the population of <i>Bacteroides</i> / <i>Prevotella</i> has been found in

CRC= Colorectal Cancer; rRNA= Ribonucleic Acid; RT-qPCR= Real Time quantitative PCR; Source: Research data, 2019.

In particular, another 25.0% (n= 3)^{19,20,23} highlighted that patients with CRC had higher levels of other species of bacteria, such as: *C. difficile*, *C. perfringens*, *Pseudomonas*, *Bacteroides* and *Prevotella*.

In relation to studies that analyzed changes in fungal composition, 16.7% (n= 2)^{17,18} observed an increase in the proportion of opportunistic fungi in people with CRC, such as *Rhodotorula* and *Malassezia* (phylum *Basidiomycota*) and *Acremonium* (phylum *Ascomycota*), which suggests that fungal markers may also be useful for detecting malignant neoplasms of the intestinal tract.

DISCUSSION

In this review, most findings showed that individuals with CRC seem to have a greater predominance of bacteria with pathogenic characteristics, with emphasis on the phylum *Bacteroidetes* and the species *Fusobacterium nucleatum*. In addition, literature was collected that pointed to a greater proportion of the *Ascomycota*: *Basidiomycota* ratio, an index that defines fungal dysbiosis, in the specific population of this study.

Dysbiosis presented itself as a potential factor to precipitate carcinogenic events and, among the aspects that support this statement, the effects of bacterial toxins, virulence factors, microbial metabolism, immune modulation and chronic inflammation stand out^{28,29}. It is worth mentioning that, the imbalance in the colonic environment is directly related to the increase in the production of free radicals and, therefore, promotes oxidative stress and DNA damage, resulting in a greater risk of developing CRC³⁰. In particular, genetic information has been the focus of approaches to these processes associated with the cancer pathogenesis in question.

According to Kinross et al²², the metagenome of these individuals has a strong association with CRC, as it is configured as the catalog of microbial genes that reside in the intestine. Some hypotheses that define these elements as key pathogens state that specific members of the low abundance microbiome may have unique virulence characteristics, or produce carcinogens, which are not only pro-oncogenic, but also modifiers of the immune response of the mucosa and cell colon epithelial, which also results in colorectal carcinogenesis.

Tjalsma et al³¹ proposed an alternative conductive passenger model for CRC, according to which the first impact of the intestinal conductive bacteria causes epithelial damage to DNA, which in turn contributes to the initiation of CRC. Consequently, the developing tumor induces changes in the intestinal niche favoring the proliferation of opportunistic bacteria, classically called bacterial passengers.

Gao et al¹⁸, Kinross et al²², Mira-Pascual et al²⁶ and Sobhani et al²⁰, for example, argued that the risk of disease was generated by the influence of characteristics of the microbial population and mainly by changes in its content. This fact was in agreement with the results of Ohigashi et al¹⁹ and reinforces the hypothesis that tumorigenesis not only modifies the microbiota, but can also appear in the already modified intestinal environment.

It is worth mentioning that many pathogenic species can interact with adhesion molecules due to these virulence factors, which guarantee invasion and damage to the intestinal epithelium³². In turn, the interaction of these substances with tissue receptors also triggers cell proliferation, activation of pro-inflammatory pathways and modifiers of genetic content²⁹. Based on this premise, microorganisms perform metabolic activities that can activate pro-carcinogenic compounds and modify inflammation pathways, increasing the expression and release of pro-inflammatory cytokines by innate immunity^{29,33}. Currently, what has been reported is that cancer patients, especially those with colon-rectum, usually show a reduction in different bacterial species, as observed in the study by Ohigashi et al¹⁹. This phenomenon results mainly from damage to the tissue immune response that compromises microbial diversity, while the increase in this variety may be a consequence of the intense irrigation of tumors and polyps²⁶.

Some researchers also report that the composition of the microbial community changes collectively and that some bacterial species have a strong and individual influence on carcinogenesis^{34,35,36}. The predominance of the *Fusobacterium* genus in neoplastic tissue, for example, indicates a high risk for CRC and can be considered a potential biomarker for the development of colorectal carcinogenesis^{22,26}.

Regarding the biological materials analyzed in the studies discussed here, it was observed that the microbiomes differed considerably, with emphasis on the fecal samples that present greater microbial load, as they gather cells from the entire gastrointestinal tract, while those from biopsies represent exclusively the microbiota of the collection site. Specifically, in the fecal material of individuals with CRC, the authors identified significant amounts of *Fusobacterium nucleatum*, while the genera *Bacillus* and *Staphylococcus* were not found. In tissue samples from patients with the same malignancy^{16,17,19,21}, on the other hand, an abundance of *Enterobacteriaceae* was observed.

It is worth mentioning that the analyses that mix several types of samples, represent important strategies to complement other parameters, mainly by the use of

more precise techniques (PCR), and to obtain a more reliable diagnosis regarding the condition and severity of the tumor. Currently, the literature recognizes fecal tests as the most common screening for CRC. However, it is still a method of low sensitivity and specificity, since it does not provide data that define high-risk groups and/or associations with different stages of this cancer¹⁹. It is worth mentioning that, in contrast, the fungal fecal microbiome has been reported as a potential predictor of CRC, and an independent parameter for assessing its risk, supported or not by clinical and biochemical indicators¹⁷. Possibly this specific characteristic of fungi stems from their ability to replace bacteria, and to increase the individual's exposure to the disease, especially due to the depletion of beneficial genera. However, findings remain inconclusive and scarce.

In this review, the results by Sobhani et al²⁰ and Wu et al²¹ highlight the increase in members of the *Bacteroides* genus in patients with CRC, possibly justified by the role they play as releasers of oncogenic toxins and promoters of a marked inflammatory response, reported in some literature. Corroborating these findings, the study by Haghi et al³⁷, which proposed to investigate the frequency of *Bacteroides* in patients with colorectal cancer, demonstrated that the presence of this genus was significantly higher in the group of cases, especially in stage III individuals of the cancer in question, compared to stages I and II. The data strengthen and substantiate the performance of these microorganisms, along with cell proliferation and the expression of specific oncogenes.

Despite the emphasis on the mentioned genus, studies still mention the significant participation of *F. nucleatum* and *B. fragilis* species in colorectal cancer tumorigenesis, modulated especially by the E-cadherin and β -catenin signaling pathways and pro-inflammatory responses^{16,27,24,25,38}. The proposed mechanism describes that *F. nucleatum* binds to E-cadherin via FadA and, therefore, potentiates the effects of β -catenin, a transcription factor common to the Wnt transduction pathway and essential for the progression of CRC (Figure 2)³⁹.

In addition, other sources indicate that *F. nucleatum* triggers the installation of the proinflammatory microenvironment and promotes the recruitment of immune cells with potential for infiltration into the tumor and negative regulation of adaptive immunity^{40,41,42}. In addition, references describe *B. fragilis* as capable of altering the epithelial structure and function and interrupting the cleavage of the tumor suppressor protein (E-cadherin), which increases the nuclear signaling of Wnt/ β -catenin and induces an increase in colon cancer cell proliferation and metastases (Figure 2)⁴³. Sobhani et al²⁰ add that *B. fragilis* species can favor carcinogenesis through the overproduction of IL-17 in neoplastic tissues, resulting in an altered immune response.

The study by Saffarian et al⁴⁴, in parallel, investigated the influence of the genus discussed in the tumor tissues of 58 patients and found that, in addition to *Bacteroidetes*

and *Firmicutes*, genera of non-fermentative environmental bacteria, such as *Proteobacteria*, comprised the colon microbiota and were involved in tumorigenic events. In particular, the species *Fusobacterium periodonticum* was more abundant in cancerous samples. Kwong et al²⁷ also observed an increase in the number of members of the *S. bovis* species, specialized in hyperproliferation and abnormal training of the colon's intestinal crypt, through the production of pro-inflammatory interleukin (IL-8). In this study, there was also an increase in the concentration of *S. gallolyticus*, antigens that can stimulate the production of various inflammatory cytokines, such as Tumor Necrosis Factor- α , IL-1b, IL-6 and IL-8 (Figure 2)⁴⁵.

Mira-Pascual et al²⁶ and Wu et al²¹, in turn, found scarce levels of *F. prausnitzii*, bacteria that produces butyrate and can lead to exacerbation of the intestinal inflammatory cascade. Likewise, Marchesi et al²³ described that butyrate acts as a protective organic acid against CRC, as it promotes a stop in the cell cycle dependent on the p²¹ protein and, consequently, increases the rate

of apoptosis of cancer cells⁴⁶. Important data related to *Malassezia* and identified in studies by Coker et al¹⁷ and Gao et al¹⁸, pointed to the increase in this fungal genus and its potential as a causative agent of CRC. Their participation is believed to involve the activation of mast cells and the release of inflammatory cytokines (especially IL-6), points that modulate the Mitogen-Activated Protein Kinase (MAPK) pathway and replicate tumor effects (Figure 2)⁴⁷.

In view of this, the findings obtained in this review did not allow for concluding that dysbiosis was a precursor to CRC, although it represented a factor that worsened the prognosis for patients, due to the positive regulation of intestinal inflammation. In addition, the studies gathered confirm that bacterial dysbiosis is associated with a high risk of adenomas and colorectal cancer, as well as that colon cancer induces a state of mucous dysbiosis, in which intestinal bacteria stimulate nutrient metabolism and production metabolome, which may precipitate the development of malignant intestinal tumors⁴⁸.

Figure 2: Mechanisms involved in the microbiota axis and colorectal pro-tumorigenic factors. Original figure authored by Thaís Rodrigues Nogueira.

It is worth mentioning that the composition and functionality of intestinal microbiota play an important role in modulating the risk of CRC. Among the various mechanisms that regulate the microbiota and effects on human health, pro-inflammatory and immunological activation in the colic mucosa, may be responsive to malignancy of the neoplasm. Likewise, the altered immune response in colon cancer tissue with overproduction of IL-17 worsens the pathological condition, mainly due to the presence of changes in microbial load²⁰. Although these aspects show that the early identification of unfavorable changes in the colonic environment of individuals susceptible to CRC can help in the prevention and treatment of the disease, the lack of clinical data that define patterns of bacterial colonization in these patients is also noteworthy.

As limiting points of this research, the following are cited: the lack of equivalence of the sample sizes of some studies, the little evidence involving the participation of fungi in the development of CRC, and as a potential bias, the fact different biological materials were analyzed.

Finally, although this critical analysis is methodologically of low evidence, the studies included with similar methodological design and adequate analytical technique allowed the discussion of relevant results and the confirmation of bacterial and fungal signatures (although with little literature) associated with colorectal cancer.

Final Considerations

It was concluded that intestinal dysbiosis is configured as a legitimate trigger for colorectal carcinogenesis, with an emphasis on specific species (*F. nucleatum* and *B. fragilis*), which demonstrated a leading role in the inflammatory cascade. On the other hand, it was found that *F. prausnitzii* is protective against tumorigenesis, mainly due to the production of butyrate. Fungi also participated in oncogenic pathways, but due to the lack of evidence on their role, it is suggested that more research be conducted to assess the effect on CRC. The results of this review provide insights for a better understanding of the effect of dysbiosis on the pathogenesis of colorectal neoplasia, which can help in establishing strategies to improve the inflammatory profile, cancer and patient survival.

Conflict of interest statement. The authors declare no conflict of interest.

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