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Literature Review

Colorectal Cancer and *Campylobacter rectus*, *C. showae* and *C. concisus*

Caroline Herløv[1]*, Stine Sloth[2] and Leif Percival Andersen[1]

[1]*Department Clinical Microbiology, Copenhagen University Hospital (Rigshospitalet), Copenhagen, Denmark*
[2]*Department of Stomach, Intestine and Liver Diseases, Herlev Hospital, Herlev, Denmark*

***Corresponding Author:** Caroline Herløv, Medical Student, Department Clinical Microbiology, Copenhagen University Hospital (Rigshospitalet), Copenhagen, Denmark.

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Abstract

The correlation between colorectal cancer and *Campylobacter* spp. was investigated in this review. 10 studies from 3 different databases were found useful to evaluate a possible correlation.

Focus has relied on the intestinal microbiome and its composition in colorectal cancer patients. Possible carcinogenic mechanisms of *Campylobacter* spp. were investigated. Studies presented in this review, showed a high incidence of *Campylobacter* spp. in the microbiome of patients with colorectal cancer.

In case of infection with *Campylobacter* spp. the permeability of the membrane in the infected cells and the stability of the cell will change with possible loss of function as a result. Due to *Campylobacter* spp. ability to induce the expression of COX-2 and IL-8 it seems that *Campylobacter* spp. possesses possible pathogenic and carcinogenic capabilities. It can be concluded that *Campylobacter* spp. are able to invade cells and cause inflammation, including IBD. In conclusion further investigation and studies are needed to verify a correlation between colorectal cancer and *Campylobacter* spp.

Keywords: *Colorectal Cancer; Microbiota; Microbiome; Carcinogenesis; Campylobacter spp*

Introduction

Colorectal cancer is the third most frequently diagnosed cancers with a higher incidence among females [1]. Colon cancer is more frequent in females, while males are more likely to develop rectal cancer. The incidence of colorectal cancer increases with the age.

Colorectal cancer is defined as a malignant tumor located in the colon or the rectum [1]. Two third of these tumors are found in colon sigmoid and rectum. These parts are located following each other in the left side of the abdomen. Adenocarcinomas, where the tumor originates from the glandular cells in colon and rectum, are the most common tumor related to colorectal cancer [1].

The etiology of colorectal cancer is not yet settled, but it is known that different environmental factors as smoking, diet and lifestyle affect the individual's risk of developing colorectal cancer [1]. Most patients are over 50 years at time of diagnosis and 75% of incidents with rectal cancer and 80% of incidents with colon cancer appear after the age of 60 years when diagnosed. A 5-year-survival differs between 90% to 10% depending on stage and other factors of the cancer [2]. Adenomatous polyposis coli or family members diagnosed with colorectal cancer at an early age are known risk factors of developing colorectal cancer [1]. Inflammatory bowel diseases as Crohn's

disease and ulcerative colitis are also known risk factors for developing colorectal cancer. The etiology depends on both genetic factors, other diseases and environmental factors [1].

It is believed that the microbiota affects the development of colorectal cancer [1]. The microbiota consists of microorganisms, bacteria and fungus which exists in the intestinal tract. The microbiota differs in each individual and its composition can affect the body in different ways [1].

The pathogenesis of colorectal cancer consists of both genetic and epigenetic deviations. The pathogenesis can proceed by different pathways where mutations will accumulate [3].

Nearly all tumors consist of a high column epithelium, similar to dysplastic epithelium found in adenomas [3]. This atypical epithelium represents an unrestrained and disorganized growth, where the cells have abnormal shape and location. The dysplastic epithelium can be considered as a precursor to cancer. The invasive component in this tumor consists of a strong stromal desmoplastic response [3].

The most important prognostic factors in colorectal cancer are the depth of the tumor's invasion in the tissue as well as the presence/absence of metastases to the lymph nodes or other organs [3]. The patient's symptoms depend on the location of the tumor - either in the colon or in rectum as well as the size of tumor and its growth into the epithelium. Most patients experience changes in their stool pattern. This can be diarrhea, constipation, or possibly mucus/blood in the stool. The patient may experience defecation pain, abdominal pain, weight loss and fatigue [2].

The treatment of colorectal cancer relies of the location of the tumor as well as the stadium of the tumor at the time of diagnosis (Table 1 and 2). Treatment of colorectal cancer include laparoscopic surgery, surgical resections and chemotherapies, both neoadjuvant and palliative. The treatment of primary disease typically consists of laparoscopic surgery. At a metastatic stage the treatment will often consist of surgical resection and if necessary this can be supplemented with radiotherapy, neoadjuvant and palliative chemotherapy [2].

TNM-classification of colorectal cancer	
Stadium	**Description**
T1	Invasion from muscularis mucosa to submucosa
T2	Invasion from submucosa to muscularis propria
T3	Invasion from muscularis propria to the outer layer of colon/rectum
T4	Invasion from colon/rectum in to peritoneum/other organs
N0	No regional metastases to lymph nodes
N1	Metastases in 1 - 3 regional lymphnodes
N2	Metastases in 4 or more regional lymph nodes
M0	No distant metastase
M1	Presence of distant metastases

Table 1: *Source [19].*

UICC Staging colorectal cancer			
Stadium	**T**	**N**	**M**
0	T is	0	0
I	T1	0	0
I	T2	0	0
IIA	T3	0	0
IIB	T4	0	0
IIIA	T1-T2	N1	0
IIIB	T3-T4	N1	0
IIIC	All stages of T	N2	0
IV	All stages of T	All stages of N	M1

Table 2: *Source [2].*

Campylobacter spp. belongs to the family of *Campylobacteraceae*. This family consists furthermore of *Helicobacter* spp., *Arcobacter* spp., and *Sulfurospirillum* spp [4]. The bacteria are curved rods with a length at 0.5 - 5 m and a width of 0.2 - 0,8 m. The bacteria are motile and will move as a corkscrew because they have one flagellum in one or both ends in the cell. However, some bacteria will be immobile because they lack flagella [4]. *Campylobacter* spp. grow under microaerobic (4 - 5% oxygen) or anaerobic conditions, where it applies respiratory and chemoorganotrophic mechanisms in its metabolism. They get their energy from tricarboxylic acid cycle or from amino acids [4]. All *Campylobacter* spp. except *C. gracilis* have oxidase-activity [4]. This type of bacteria are not able to utilize carbohydrate in the growth medium (non-fermenters). *Campylobacter* spp. has a temperature-optimum relative to growth at 30 to 37, whereas thermophilic *Campylobacter* spp. (*C. jejuni, C. lari* and *C. coli*) have a temperature-optimum relative to growth at 42 - 43 [4,18].

Most *Campylobacter* spp. are found in the gastrointestinal tract, in the oral cavity and in the reproductive organs of humans and animals [4]. Some of these *Campylobacter* spp. are pathogenic for humans and animals [4]. It is easy to culture the thermophile species in a microaerobe atmosphere on a selective medium and not necessarily with use of hydrogen. When culturing more rare species (atypical species) it is necessary to use the completely appropriate growing conditions in the medium to obtain growth [4]. It can be difficult to distinguish the different *Campylobacter* spp. biochemically because the diversity often constitutes of one single factor, such as the presence of hippuricase or urease activity [4]. Previously biochemical methods were used to identify the bacteria, but now molecular biological techniques such as specific polymerase chain reaction (PCR), 16S rRNA-sequencing and next generation sequencing (NGS) are used [5].

C. rectus thrives in an anaerobe environment and it requires hydrogen. *C. rectus* is found related to appendicitis, in periodontal pockets, in extra-oral abscesses and in patients who suffer from Barrett's esophagus. *C. rectus* is called a "presumed periodontally pathogen" [4]. *C. concisus* grows in a microaerobic environment and requires hydrogen for optimal growth conditions. *C. concisus* is found in periodontal pockets in patients with periodontitis and gingivitis. *C. concisus* has also been found in blood and stool samples from patients with and without diarrhea as well as in patients who suffer from Barrett's esophagus. This review relies on two atypical *Campylobacter* spp. - *C. rectus* and *C. concisus*. These are selected because they are some of the most frequent atypical *Campylobacter* spp. found in humans.

Common culture methods have been corrected towards the thermophile *Campylobacter* spp., which are relatively uncomplicated to grow. Therefore, these species are well examined. In this review the atypical *Campylobacter* spp. were chosen, because they are more complicated to culture and, therefore, examined to a lesser extent. These species do not cause the typical pathogenic mechanism in the gastrointestinal tract, but is assumed to have a bigger impact in the development of diseases for example in immunosuppressed patients [18].

Aim of the Study

The aim of this study was to investigate a possible correlation between colorectal cancer and *Campylobacter* spp. This is investigated in studies about the microbiota and in studies concerning mechanisms to carcinogenesis.

Methods and Databases

Three different databases, PubMed, Embase and PMC were used for the search on colorectal cancer and *Campylobacter* spp. This string was designed to find studies, which illuminates a possible correlation between colorectal cancer and atypical intestinal *Campylobacter* spp. with specific focus on *C. rectus*, *C. concisus* and *C. showae*.

Relevant information was found in 10 studies [7-16], where 6 studies exclusively are found in PMC, 2 are found in both PMC and Embase, 1 is found in PMC and PubMed and the last one is found in all of the 3 databases. This illustrates that the 3 databases differ in search results. In the examination of the relevant studies' reference lists, one study was found relevant [16].

Of the 10 selected relevant studies, 3 of them discuss the microbiome [7,9,15]. 7 discuss mechanisms of carcinogenesis [8,10-14,16]. The microbiome studies describe compositions of the microbiome found regarding colorectal cancer and *Campylobacter* spp. The stud-

ies related to mechanisms to carcinogenesis describe directly, how *C. rectus, C. showae* and *C. concisus* affect the tissue and the cells via mechanisms, which possibly can lead to carcinogenesis.

Results and Discussion

Three studies describing the microbiome in colorectal cancer were identified. In all three studies bacteria which normally belong to in the oral microbiome were found in the intestinal microbiome, including *C. concisus*, *C. rectus* and *C. showae*. In the study by Zhang., *et al*. [7] an increased level of *C. rectus* was found in the intestinal microbiome from patients with colorectal cancer. They describe a correlation between microbes associated with colorectal cancer and inflammatory factors. *C. rectus* is shown to contribute to the recruitment of inflammatory factors. A microenvironment favorable for the development of colorectal cancer is formed by the microbiome and inflammation in conjunction, where *C. rectus* constitute as a risk factor. In the other two studies [9,15] *C. rectus*, *C. concisus* and *C. showae* were found. *C. showae* was clearly overrepresented in the study by Warren., *et al*. [9] However, overrepresentation of *C. showae* could indicate relevance for further investigation of *C. showae* and colorectal cancer.

Co-occurrence of *Fusobacterium nucleatum* and *Campylobacter* spp. are described in two of the studies [9,15]. A number of studies describe a correlation between *F. nucleatum* and colorectal cancer [23-25]. Its co-occurrence with *Campylobacter* spp. is found in colorectal carcinomas. This finding raises the question if *Campylobacter* spp. can be directly associated to colorectal cancer because of the co-occurrence with *F. nucleatum* which is known to contribute to the development of colorectal cancer [26,27]. These bacteria are normally found in the oral microbiome and in patients with oral leukoplakia. This may indicate an association between the patient's oral health and the risk of developing colorectal cancer.

Seven studies describing mechanism of carcinogenesis related to *Campylobacter* spp. was identified [8,10-14,16]. The first studies describe *Campylobacter* infection to cause damage to the epithelium and an increase in the inflammatory response. In the study by Gemmell., *et al*. [8] a zonula occludens toxin and exotoxin 9 production by *C. concises* were found. By disturbing tight junctions in the epithelium zonula occludens toxin increases the intestinal permeability and exotoxin 9 possesses characteristics which damage the epithelium. This increases the pathogenic potential, which in this study is concluded as tribe specific [8]. In the study by Deshpande., *et al*. [10] the intestinal epithelial cell line Caco-2 was exposed to adherent toxigenic *C. concisus* and adherent invasive *C. concisus*. As in the study by Gemmell., *et al*. [8] infection with *C. concisus* caused damage of the epithelium. The infection affects transcripts to be upregulated or downregulated. Processes related to epithelial to mesenchymal transition was intensified. Transcripts related to autophagy and processes related to cell-cycle and DNA-repairing were downregulated, which create an increased risk of dysfunctional cells. An infection will enhance the cells pathogenic potential by inducing their instability. In a study by Kaakoush., *et al*. [11] several transcripts changed with either downregulation or upregulation as a cause of the infection. Overall an increase in the inflammatory response was seen. Further, two microRNA's (MIR146A and MIR221) were increased in colorectal cancer tissue. As in the studies of the microbiome this study also describes an overrepresentation of *C. concisus* in colorectal cancer patient's microbiome and in colorectal carcinomas. The first studies raise the question if *Campylobacter* spp. can be correlated to colorectal cancer because it possesses mechanisms similar to mechanisms of carcinogenesis and "Hallmarks of cancer". Upregulated colorectal cancer associated microRNA's in patients with *C. concisus* infection might indicate a possible correlation between colorectal cancer and *C. concisus.*

In the study by Ovesen., *et al*. [12] *C. concisus* infection was found to increase its motility and its ability to form biofilm under microaerobic conditions. The metabolism and growth were decreased under anaerobic conditions. In this study patients with inflammatory bowel disease (IBD) were one of the patient groups to be investigated. The inflammatory environment in IBD-patients with increased level of oxygen is a favorable environment for *C. concisus*. This can explain the overrepresentation of *C. concisus* in IBD-patients [12]. IBD dispose to colorectal cancer [6]. *C. concisus* could also dispose to colorectal cancer because of the correlation between IBD and colorectal cancer. A study by Lee., *et al*. [13] describes the association between periodontitis and colorectal cancer. Periodontitis is described to dispose to IBD [13] and IBD is described to dispose to colorectal cancer [6]. This raises the question whether it is possible that periodontitis

disposes to colorectal cancer. In this study a higher incidence of colorectal adenomas was found in patients with periodontitis [13]. This might indicate an association between the patient's oral health and the risk of developing colorectal cancer.

In the study by Ismail., *et al*. [14] and the study by Man., *et al*. [16] an increase in the inflammatory response and an increase in the production of COX-2 was described. COX-2 is often related to inflammation and IBD. In a study by Thun., *et al*. [17] COX-2 found an association between colorectal cancer and *Campylobacter* spp. In both studies [14,16] IL-8 was upregulated, which might indicate that IL-8 plays a role in the development of colorectal cancer. Warren., *et al*. [9] an induced level of IL-8 was found. In a review by Ning., *et al* [2]. IL-8 is emphasized in several studies to be one of the most upregulated cytokines related to colorectal cancer. IL-8 causes an inflammatory response and furthermore it can affect the cancer cells via receptors. This leads to increased migration, proliferation, invasion and initiation of angiogenesis. IL-8 is found in increased levels in patients with *C. concisus* infection [14]. These results may indicate that *C. concisus'* ability to induce the expression of IL-8 can result in an increased risk of developing colorectal cancer.

Thus, *Campylobacter* spp. possesses possible carcinogenic characteristics, which can lead to the development of colorectal cancer. In the 10 studies [7-16] different methods were used and, therefore, the results are not directly comparable. Despite the different methods similarities between the studies were found. Two studies [9,15] describe, how *Campylobacter* spp. and *Fusobacterium* spp. co-aggregates in relation to colorectal cancer. Further, an increased level of IL-8 in relation to *C. concisus* infection was found in three studies [9,14,16].

Conclusion

These microbiome studies found both presence and increased levels of *Campylobacter* spp. in the composition of the microbiomes from colorectal cancer patients. This may indicate a possible correlation between the composition of the microbiome and patients' risk of developing of colorectal cancer. In addition, *Campylobacter* spp. possesses possible carcinogenic characteristics, which can lead to the development of colorectal cancer. Further investigation is necessary to finally verify this. In the future it would be interesting to investigate the correlation between the occurrence of specific *Campylobacter* spp. in patients with colorectal cancer, polyps and in patients without cancer risk factors as a clinical case-control study on humans.

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