DOI: 10.7860/JCDR/2024/60755.18860

Review Article

Internal Medicine Section

Role of Intestinal Microbiota in the Pathogenesis of Colorectal Cancer: A Narrative Review

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ABSTRACT

The human gut microbiota forms a biome and acts as a neglected organ, playing vital roles in organ integrity, metabolism, immunity, and homeostasis. Variations in the microbiome can lead to disease initiation. Research using bacterial sequencing of faeces and digestive tissues has focused on understanding the role of gut microbiota in cancer development, particularly Colorectal Cancer (CRC), Dysbiosis and modifications in the intestinal microbiota have been observed in CRC cases. Hypotheses like the alpha bug hypothesis and the driver-passenger model aim to explain the correlation between gut microbiota and CRC pathogenesis. The present article summarise the functions of gut microbiota, mechanisms involved in colorectal carcinogenesis, and discusses the clinical significance of gut microbiota in CRC screening and therapy.

Keywords: Diet, Dysbiosis, Gastrointestinal malignancy, Inflammation, Screening

INTRODUCTION

Colorectal Cancer (CRC) is considered to be one of the common and deadliest types of cancer. It ranks third in recurrence and fourth in cancer-related mortality, causing nearly 700,000 deaths annually [1]. Among males, CRC is the third most frequent cancer, while among females, it is the second most common [2]. The majority of cases of CRC are reported in Western countries, with a yearly exponential increase [3]. Factors such as lifestyle, chronic diseases, and age significantly influence the likelihood of developing CRC [1].

The human gut harbours a vast number of microorganisms, exceeding the total count of human cells [4]. This microbial community interacts with the host to maintain homeostasis. The intestinal microbiota to play a pivotal role in the energy production, stimulates the intestinal epithelium, enhances pathogen defense, and triggers IgG antibodies [5]. Gut microbiota is established early in life, acquired from the mother's vagina and skin, and remains stable throughout one's lifetime [6]. Factors like medication, diet, exercise, and genetics influence the growth and stability of gut microbiota [7].

Destruction of the gut microbiota can havoc the normal physiological functioning, leading to various diseases [8]. Recent studies on microbiota and colonic carcinoma have revealed a significant relationship, analysing the role of gut microbiota in CRC [9,10]. These studies have compared the microbial composition of patients with colorectal carcinoma to that of healthy individuals, identifying differences in microorganism abundance and depletion [9,10].

The CRC typically originates from abnormal and uncontrolled growth of the cells lining the colon or rectum. It often begins with the formation of benign mucosal growth called a polyp. Adenocarcinoma of the colon is the most common malignancy in the Gastrointestinal (GI) tract and is recognised as the leading cause of morbidity and mortality worldwide [11].

Present study review aims to highlight the significance of intestinal microbiota in the human body, summarise relevant findings, explore the association between gut microbiota and colonic carcinoma, and discuss the potential use of gut microbial changes as biomarkers for early diagnosis and prompt treatment.

Incidence of Colorectal Cancer (CRC)

According to Global Cancer Observatory (GLOBOCAN) 2018, colonic carcinoma ranks fourth in incidence, while carcinoma of the rectum ranks eighth, making CRC the third most prevalent cancer globally [12]. In 2018, approximately 1,096,000 new cases of colon cancer and 704,000 new cases of rectal cancer were reported [13]. CRC is more common in males than females [11]. It is about 25% more prevalent in developed countries compared to developing countries, suggesting a potential association with lifestyle patterns [13]. Northern and Southern European countries, New Zealand, have higher rates of colonic cancer, while rectal cancer is more dominant in Eastern Asia, New Zealand, Australia, and Eastern European nations. North America has the highest number of reported cases for both colon and rectal cancer [14]. Hungary has the highest reported cases of CRC per 100,000 population among males, and Norway leads among females. African and South Asian countries reported fewer cases of rectal and colon cancers [14]. In 2018, CRC ranked as the second most common cancer globally [Table/Fig-1] [15], with 881,000 deaths. Colon cancer alone accounted for 551,000 lives, making it the fifth most fatal cancer, while rectal cancer claimed 310,000 lives, ranking it as the tenth most deadly cancer worldwide [13]. The predicted five-year prevalence of CRC in India is 87 per 100,000 people. The low incidence of CRC in developing countries is believed to be influenced by variations in dietary habits and lifestyles. Additionally, there are differences influenced in the prevalence of obesity, a risk factor for CRC, between the developed and developing worlds. A study conducted by Patil PS et al., suggests another factor that contributing to the lower prevalence of CRC in the younger population, compared to the elderly, could be age-related factors [16].

Cancer	Percentage of cancer-related deaths
Lung	18.04%
Colorectum	9.39%
Liver	8.34%
Stomach	7.72%
Breast	6.88%
Oesophagus	5.46%
Pancreas	4.68%

[Table/Fig-1]: Cancer-related deaths in 2020.

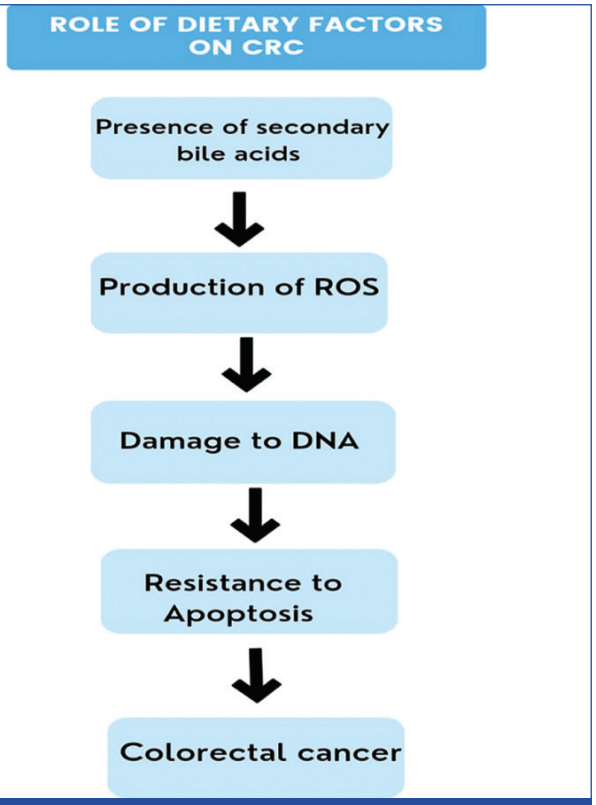
Aetiology

Majority of the cases of CRC have a sporadic origin, with about 20% of patients exhibiting a positive family history on average. Genetic and environmental factors together contribute to the

development of CRC. Conditions such as Lynch syndrome and serrated polyposis are closely associated with CRC [17]. Familial adenomatous polyposis, caused by mutations in the adenomatous polyposis coli gene, is another prevalent syndrome linked to CRC. Patients with familial adenomatous polyposis develop multiple colorectal adenomas that progress to CRC at a young age [18]. The risk of CRC is significantly increased in individuals with Inflammatory Bowel Disease (IBD), and this risk is proportional to the duration of IBD. However, only 1% of CRC cases are associated with IBD. Recent studies suggest that the prevalence of CRC in IBD patients is decreasing due to advancements in modern medicine and effective anti-inflammatory treatments [19,20].

Various environmental factors play a crucial role in the development of CRC. Fortunately, these factors, particularly lifestyle factors, can be modified through self-discipline and following a strict regimen. Smoking and alcohol consumption increase the risk of CRC. Moderate alcohol consumption is associated with a 25% increased risk of CRC, while higher alcohol consumption raises the risk to 50% [21]. Similarly, heavy smoking shows a similar trend. Increased Body Mass Index (BMI) is another factor that predisposes individuals to CRC. With each unit increase in BMI, there is an almost 3% increase in the risk of CRC [22]. A sedentary lifestyle is also a major contributing factor. Daily physical activity, for at least 30 minutes, has been shown to decrease the risk of CRC [23]. A well-balanced diet, rich in fibre, may help reshape the organisational structure of the gut microbiota and improve its function, thereby controlling metabolite production and promoting colonic health. The consumption of red and processed meat significantly increases the risk of colon cancer [24]. The carcinogenic effects associated with red meat consumption may be attributed to the use of preservatives, additives, or chemicals in its preparation and cooking. Gut bacteria metabolise these compounds, creating molecules that contribute to the development of CRC.

Furthermore, a high-calorie diet is directly linked to an increased risk of colon cancer. Studies have shown higher levels of deoxycholic acid in CRC patients [Table/Fig-2] [25]. Patients with gallstones also have higher concentrations of secondary bile acids and are at an increased risk of CRC [26].



[Table/Fig-2]: Role of dietary factors on development of CRC.
CRC: Colorectal cancer

On the other hand, consumption of vitamin D, fresh fruits and vegetables, multivitamins, calcium, milk, whole grains, and fibre is associated with a decreased incidence of CRC [25]. Therefore, a shift towards consuming organic vegetables is strongly recommended. The association between dietary fibre consumption and decreased CRC risk is supported by observations of significantly lower numbers of CRC cases in African populations that consume a high-fibre diet [27]. Dietary fibre can exert an anti-CRC effect, potentially due to its impact on gut microbiota. The bacteria in the gut ferment fibre to produce short-chain fatty acids, which play essential roles in regulating of metabolism and the immune system and lower the risk of CRC. Similarly, whole grains also exert their effects through the production of short-chain fatty acids. They also contain beneficial nutrients like flavonoids and polyphenols, which act as the key modulators of gut microbiota [28]. These lifestyle factors contribute to the geographic and socio-economic differences in the occurrence of CRC.

Gut Microbiota

Gut microbiota refers to the collection of microorganisms, including bacteria, viruses, fungi, and other organisms, that reside in the Gastrointestinal Tract (GIT), which plays a role in maintaing the gut homeostasis. Gut microbiota has coevolved with the host and the adult human gut is inhabited approximately 100 trillion microorganisms, with considerable variation in the type and number of microorganisms along the length of the GI tract, from the mouth to the rectum [29]. Bacteria make up about 70% of the microbiome. Microorganisms are classified as luminal, faecal, or mucosa-associated flora based on their location [30].

The precise number and composition of microorganisms in the human gut vary depending on the host's lifestyle and genotype [31]. Firmicutes, Bacteroidetes, and Actinobacteria are the three primary phyla whose bacteria I species are commonly found in the human gut. Bacteroides, Bifidobacterium, Atopobium, Peptostreptococcus, Eubacterium, and Fusobacterium are predominant obligate anaerobes in the intestinal microbiota. In contrast, facultative anaerobes like Enterobacteriaceae, Enterococci, Lactobacilli, and Streptococci make up a smaller portion. The composition of bacteria varies significantly along the gut [Table/Fig-3] [32], with Bacteroidetes and Actinobacteria comprising over 90% in the colon but only 50% in the small intestine. Firmicutes species constitute around 40% [29].

Part of GIT	Bacteria per gram content
Stomach	10^1
Duodenum	10^3
Jejunum	10^4
Ileum	10^7
Colon	10^{12}

[Table/Fig-3]: Bacterial content in different parts of Gastrointestinal Tract (GIT).

Functions of Gut Microbiota

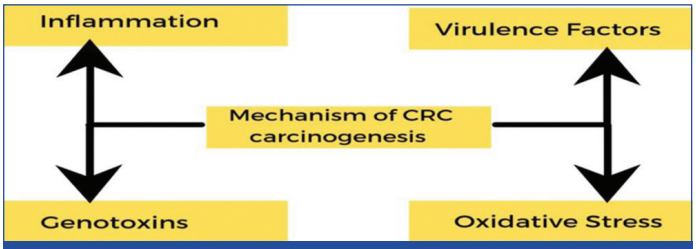
Gut microbiota plays a crucial role in the development and function of the mucosal immune system, nutrient absorption, angiogenesis, and the enteric nervous system. It also affects epithelial homeostasis, wound healing, and cell renewal [33-35].

The microbiota synthesis essential vitamins such as B12, folate, thiamine, nicotinic acid, vitamin K, biotin, pyridoxine, riboflavin, and pantothenic acid. Additionally, it ferments complex carbohydrates to produce Short-Chain Fatty Acids (SCFAs) like acetate, butyrate, and propionate [36]. SCFAs they regulate various cellular processes, have anti-inflammatory and anticancer effects, provide energy for colonocytes, and enhance gut barrier function. Propionate impacts human eating patterns and gluconeogenesis, while acetate and butyrate are involved in lipid formation. SCFAs also stimulate the

synthesis of IL-8, which helps maintain epithelial integrity. Added to the functions mentioned above, gut microbiota prevents the colonisation of pathogens and guarantees "colonisation resistance" [37].

Function of gut microbiota in colorectal carcinogenesis: Presently, the vogue has been put into investigating the functioning of intestinal microbiota in CRC carcinogenesis. An interesting point to note is that the colon contains one-million-fold more bacteria than the small intestine, and it is estimated that there is 12-fold more cancer developing in the colon than in the intestine, indicating a possible link between intestinal microbiota and CRC [38]. A critical hypothesis of CRC carcinogenesis is the concept of microbial dysbiosis [39]. However, whether dysbiosis is a cause or consequence is still a conundrum among researchers. Few bacterial species, like Streptococcus Bovis, Escherichia coli, Enterococcus faecalis, and Fusobacterium spp., have been recognised, probably suspected to contribute to colorectal carcinogenesis [30].

The CRC can arise from one or a combination of four different mechanisms, namely inflammation, the effect of genotoxins, virulence factors, and oxidative stress [Table/Fig-4].



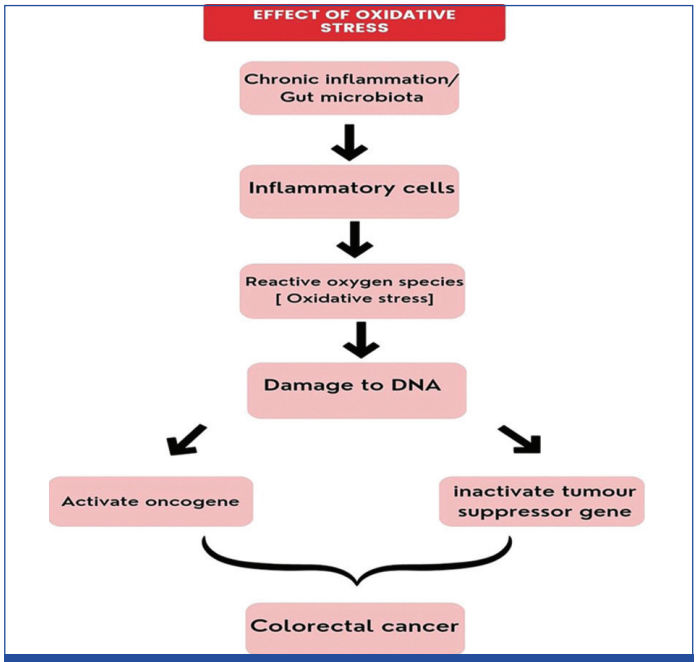
[Table/Fig-4]: Mechanism of colorectal carcinogenesis.
CRC: Colorectal cancer

Inflammation: Studies suggest and shows an evidence of a clear link between inflammation and tumourigenesis [40]. The intestinal microbiota is separated from the immune cells by a mucosal barrier, which is formed by a single sheet of enterocytes attached together by tight junctions forms the intestinal mucosal barrier [41]. The intestinal mucosal barrier appears to become more permeable in CRC patients [42]. This damage is caused by dextran sodium sulphate-induced colitis and ablation of a membrane-bound protease called matriptase. As a result, the altered IECs cannot create a strong mucosal barrier, allowing bacteria and their breakdown products to invade the tumour stroma. F. nucleatum and P. anaerobius play a part in developing CRC by fostering an inflammatory microenvironment [42].

Virulence factors: A prerequisite for bacteria to cause tumourigenesis is their ability to attach to the mucosal surface. F. nucleatum attaches to the mucosal surface with the help of Fusobacterium adhesin A (FadA), which, in turn, binds particularly to E-cadherin and produces an oncogenic response [43]. F. nucleatum also prevents T cell activation with the help of its surface adhesin. P. anaerobius contains a surface protein known as putative cell wall binding repeat 2, which attaches to enterocytes and initiates tumour cell proliferation. S. bovis, whose number is found to be increased in CRC cases, contributes to carcinogenesis by inflammation. The AvrA protein in Salmonella causes tumourigenesis by activating STAT3 signalling and β-catenin pathways in tumour cells of the colon [44].

Genotoxins: Genotoxins produced by gut microbiota strongly affect colorectal carcinogenesis due to their DNA-damaging effects. E.coli produces colibactin, which promotes the senescence of cells and the proliferation of tumour cells [45]. Typhoid toxin produced by Salmonella damages the DNA of colonic epithelial cells through the PI3K pathway [46].

Oxidative stress: The imbalance between the generation of pro-oxidative molecules and the efficiency of antioxidant defenses is known as oxidative stress. Chronic inflammation causes inflammatory cells to produce a large amount of reactive oxygen species, which can lead to Deoxyribonucleic Acid (DNA) damage, further activate oncogenes, or deactivate tumour-suppressor genes, accelerating the development of CRC [Table/Fig-5]. Reactive oxygen species can potentially be directly produced by the gut microbiota. Infected macrophages with E. faecalis produce superoxide, which harms epithelial cell DNA. E. faecalis can create hydroxyl radicals, which are potent mutagens that lead to DNA mutations which, increasing the risk of chromosomal instability and CRC [47].



[Table/Fig-5]: Role of oxidative stress in the development of Colorectal Cancer (CRC).

A significant worth mentioning is the association of the faecal bacterium prausnitzii with CRC. It is a commensal bacterium that has anti-inflammatory effects. It exerts its anti-inflammatory action by reducing the number of interferon-gamma [48].

Clinical Significance of Gut Microbiota

Application in screening: Intestinal microbiota can be utilised in the screening of CRC [49]. Various studies show that the gut microbiome exhibits explicit alterations in adenomas and carcinomas [4,9,30]. The presence of particular bacteria helps in understanding the disease state and its prognosis to some extent. For example, a higher amount of Fusobacterium nucleatum is seen in high-grade dysplasia and is associated with a shorter survival duration [50].

Therapeutic application: Gut microbiota also exhibits promising contributions in cancer therapy. Bacteroides fragilis has been shown to improve treatment results by activating T cells. Bifidobacteria, by targeting CD8+ T cells, help prevent tumour growth [51]. These possible mechanisms give us hope in taking cancer treatment a step forward. However, further exploration deep into microbes and their probiotic effects has to be studied thoroughly.

CONCLUSION(S)

Colorectal Cancer (CRC) is considered one of the most prevalent forms of cancer worldwide and the third most common malignant cancer. Recently, there has been significant focus on investigating the functioning of the intestinal microbiota in CRC carcinogenesis. Gut microbiota plays a pivotal role in the health and disease processes in human beings. The composition of microorganisms exhibits observable changes during the course of an illness. Extensive studies to understand the mechanism of tumour promotion and microbial co-existence in CRC help to solve the conundrum of whether dysbiosis is a cause or consequence of the disease. Further research on the exact relationship between intestinal microbiota and metabolic by-products associated with the adenoma-carcinoma sequence could lay the foundation for more therapeutic approaches to prevent and better manage CRC.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Oct 17, 2022
- Manual Googling: Nov 29, 2022
- iThenticate Software: Feb 27, 2023 (16%)

ETYMOLOGY: Author Origin

EMENDATIONS: 6

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was informed consent obtained from the subjects involved in the study? No
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Oct 15, 2022**
Date of Peer Review: **Nov 24, 2022**
Date of Acceptance: **Feb 23, 2023**
Date of Publishing: **Jan 01, 2024**