Introduction

Colorectal cancer (CRC) is a term used for either cancer found in the colon or cancer found in the rectum [1]. Colon cancer is characterized as a tumor of the large intestine and rectal cancer is a type of colon cancer that is found distally in the colon, which is called the rectum [1]. CRC is usually initiated in the epithelial cells of the large intestine [2-4]. These growths, known as polyps, proliferate in this area when certain cells of the epithelium selectively mutate [2-4]. With accelerated replication of these cells, a benign adenoma may develop, which can then evolve and progress into a carcinoma, or invasive cancer, over a period of time, sometimes spanning 10-20 years [2-4]. Colorectal cancer is a diverse process involving alterations influenced by diet, environmental exposures, microbial changes, and host immunity [5]. There is growing evidence for CRC manifesting from disturbance in gut microbiota composition, as influenced by food and dietary intake [6]. For example, gut microbiota dysbiosis can promote chronic inflammatory conditions, leading to production of carcinogenic metabolites, and subsequently neoplasia or as previously indicated, polyps [7]. The colon contains hundreds of species of microbiota that aid in the breakdown of undigested protein and starch components [7,8].

Intestinal microbiota have key roles in the colon including metabolizing undigested food components, synthesizing nutrients like folate, biotin, niacin, and vitamin B12 [6], modulating the immune response, secreting antimicrobial products, and signaling for epithelial cell renewal [9]. With research showing that 95% of colorectal cancers are sporadic in regards to their genesis, occurring in individuals without familial predisposition, etiology of colon cancer continues to be investigated including the possible association with gut microbiota [10].

Prevalence and Incidence of Colorectal Cancer

Globally, CRC is of great concern, as the third most commonly diagnosed cancer and the second most deadly cancer in the world [7]. This represents a growing public health burden as CRC cases are expected to increase by 60% over the next decade, reaching 2.2 million new cases and 1.1 million annual deaths by the year 2030 [7]. Colorectal cancer is characterized as a western disease with high rates of incidence in North America, Australia, New Zealand, and Europe, as compared to low rates of incidence in rural African and Asian countries [6]. The variation noted geographically for this disease adds evidence to the argument that socioeconomic-associated environmental factors, including sedentary lifestyle, increased rates of overweight and obesity, and dietary consumption patterns of excessive red, processed meats coupled with low dietary fiber, are a leading cause for the development of CRC, with...
incidence 3-4 times higher in developed nations compared to developing nations [6,11].

Role of Diet in Colorectal Cancer Incidence

Dietary intake has an effect on the development of colon cancer. Studies show that consuming a diet high in red meat and processed meats, coupled with low intake of fruits, vegetables, and dietary fiber, common traits of a Westernized diet, increase risk for colon cancer [7,12,13]. Studies also suggest that consuming increased amounts of calcium and fiber in the diet may play a role in reduction of colon cancer as well [14].

Meat consumption, specifically red and processed meat, saturated fat, and alcohol consumption may lead to an increase in the susceptibility to develop CRC [12]. While additional research is needed to determine causal links between meat and colon cancer, one possible explanation is the presence of heterocyclic amines (HCAs) produced when meat is cooked at high temperatures [15]. Another explanation is that the addition of nitrates in processed meats contribute to this connection, as nitrates are converted to nitrosamines in the body, which have been found to be carcinogenic [15]. Additional evidence for diets high in meat content to contribute to colon cancer risk includes evidence that N-nitroso compounds (NOCs) are present in the cells of individuals consuming high meat diets, with NOCs being recognized as potentially carcinogenic with the ability to induce DNA changes [16].

Dietary fat intake, specifically a diet high in saturated fatty acids, may have a relationship in development of colon cancer, though it is not conclusive [6]. From the cohort Nurses’ Health Study, saturated animal fat intake was shown to be positively associated with colon cancer incidence in women [17]. Despite this positive association, it was noted that fat intake was not assessed independently of total energy intake in the study [17]. A possible indirect effect on colorectal cancer has been associated with the stimulatory effect of hepatic bile acid synthesis by a high-fat diet, which results in larger amounts of bile acids escaping the enterohepatic circulation and entering the colon [18]. During this process, they increase the amount of microorganisms responsible for their conversion to secondary bile acids [18]. Experimental evidence indicates that secondary bile acids, namely lithocholic and deoxycholic acid, may be carcinogenic to the colon [19]. As research in this area continues to emerge, findings suggest that from a mechanistic standpoint, a high-fat diet might increase risk for colorectal cancer through its effects on inflammation, gut microbiota, stem cell regulation, and prostanoid metabolism [6].

Research has shown that moderate to heavy alcohol consumption is associated with 1.2- to 1.5-fold increased risks of cancers of the colon and rectum compared with no alcohol consumption [20]. Possible mechanisms behind this association of increased risk include the carcinogenic contaminants in alcoholic beverages including nitrosamines, asbestos fibers, phenols, and hydrocarbons [21]. Metabolism of ethanol to acetaldehyde may damage DNA and generate reactive oxygen species which also cause DNA damage [21].

There are some foods in the diet that have been shown to have protective effects against colon cancer. Fruits and vegetables, with a high fiber content, antioxidant properties, and phytochemical composition, are foods which contain components that help to reduce CRC risk [22]. Studies have shown an inverse relationship between antioxidant capacity and colorectal cancer risk, as well as the anti-inflammatory effects of vitamins A and C, found abundantly in fruits and vegetables [22]. Fiber, also found in fruits, vegetables, and whole grains, has demonstrated protective effects against colorectal cancer most likely related to its effects on gut microbiota [13]. In the large intestines, fiber from the diet is fermented by bacteria which then produce short-chain fatty acids (SCFAs). These SCFA in turn help to regulate both the immune system and metabolism, which has beneficial effects on health, reducing colon cancer risk [13]. Low dietary intake of fiber may affect the intestinal microbiota by influencing cell physiology, cell homeostasis, or energy metabolism [23]. These changes impact inflammatory response and may lead to the chronic inflammatory state of colorectal cancer [23].

Studies have associated calcium as a nutrient of interest in risk for colon cancer [14]. Many epidemiological studies have found that calcium may have a protective effect, including a cohort study investigating the relationship between calcium intake and colorectal cancer risk [24]. In the Wu K et al study, data from both the Nurses’ Health Study and the Health Professionals Follow-up Study were combined, finding that individuals with a calcium intake of more than 700 mg per day had a 35%-45% reduced risk of colon cancer, specifically of the distal part of the colon, than study participants whose calcium intake was 500 mg or less per day [24]. Some studies have described a protective effect including the results the research of Yang W et al finding a causal relationship between higher calcium intake and lowered colorectal cancer risk [25]. They further described the calcium-sensing receptor (CASR) mediating an antineoplastic effect from calcium [25].

Effect of Diet on the Gut Microbiota

Gut microbiota is a term to describe the trillions of microorganisms that encompass the microbiome, or the internal environment associated with health and disease [26]. The gastrointestinal tract, populated by various microorganisms, includes 1,000-1,500 species of bacteria that help direct maintenance of intestinal homeostasis [27]. Also important to the GI tract, gut microbiota participate in regulation of tissue development as well as maintenance of the mucosal barrier [26,27]. Gut microbiota has also been implicated in generating short-chain fatty acids, involved in metabolic processes, and has played a role in immune and...
inflammatory responses [28]. Gut microbiota has a unique composition per each individual and while the microbiome has been shown to remain relatively stable over the lifespan, diet has been identified as a key modifiable factor leading to manipulation of gut microbiota composition, stability, and diversity [29]. Studies continue to investigate the extent of these alterations to determine how transient or permanent they may be [29].

Gut microbiota has been shown to be complex in nature. Evidence has shown that some microbiota are beneficial in nature, improving digestibility of nutrients, helping to maintain normal gut function, and providing essential nutrients the body needs [30]. The gut microbiome is also influenced by dietary intake of highly processed foods, leading to dysbiosis in the microbiota composition, which promotes inflammation and metabolic disturbance [31]. Research also suggests that intestinal dysbiosis plays a role in promoting disease and is considered a component in regulation of metabolism [30]. With an impact beyond intestinal health, gut microbiota and its influence on health-related disease has been identified as an element needing further investigation. In particular, diet has been identified as a modifiable factor in the composition of microbiota [30].

**Gut Microbiota and Tumorigenesis of Colorectal Cancer**

Diet has been identified as a lifestyle factor associated with risk of development of colorectal cancer. Because diet is also a key modifiable factor of gut microbiota, research in the area of gut microbiota and colorectal cancer has emerged as a relationship of interest. Research has established that the presence of gut microbiota plays a key role in inflammation present in the large intestines, which has been associated with the development of colorectal cancer [32]. Understanding of the exact mechanism of action remains to be determined, however individuals diagnosed with inflammatory bowel diseases like Crohn’s disease and ulcerative colitis, who experience chronic inflammation have been noted with an increased incidence of colorectal cancer [33]. Inflammation that is brought on by gut microbiota can influence tumorigenesis related to impaired intestinal barrier function, influencing bacterial translocation, and inducing cytokine action [34]. Grivennikov SI et al. found that an impaired intestinal barrier results in microbes entering the adenoma, which elicits inflammatory cytokines, resulting in enhanced tumor growth [35].

Bacterial species including *Firmicutes, Bacteroidetes, Actinobacteria,* and *Proteobacteria* are found abundantly in the gastrointestinal tract [36]. Pathogenic changes can occur in microbiome composition, as a result of factors like diet or host genetics, shifting a neutral microbial environment to dysbiosis, which induces inflammatory processes associated with disease [36]. In the microbiome, there are a number of different bacterial populations that have an influence on colon carcinogenesis with the potential to produce carcinogenic toxins and to incite an inflammatory response, including *Escherichia coli, Bacteroides fragilis,* and *Fusobacterium nucleatum* [24,37,38]. While these individual bacteria can work singularly, more likely, there is a collective effect from microbiota within the microenvironment working in conjunction and interacting in ways that influence tumorigenesis [38]. Research has linked obesity to the onset of dysbiosis of the gut microbiome, which is noted to be pathogenic changes in microbiome profile and functions, and has also been linked to an increased risk for development of colorectal cancer [28]. *Firmicutes* is one bacterial species associated with obesity as well as a decrease in overall microbial abundance and diversity [28]. *Fusobacterium nucleatum,* from the bacterial lineage of *Firmicutes,* has been identified as a bacterial species associated with colorectal carcinogenesis and has been found to advance the spread of colorectal cells and increase tumor growth rates [39,40]. Rubinstein MR et al. has shown that *Fusobacterium nucleatum* is able to attach and invade the intestinal epithelium through FadA adhesion protein and further evidence has shown that this bacterium can bind to inhibitory receptors that suppress immune cell activity [41,42] (Figure 1).

Also to be included in the discussion of gut microbiota and colon cancer is that some bacterial populations present in the colon may have a protective effect, mediated through three possible mechanisms [38]. Certain gut microbes have the potential to compete with pathogenic bacteria and act in a tumor-suppressive role [43]. This protective effect may also be facilitated through either metabolite production or enhancement of the immune response [43]. Fermentation products of gut microbiota including butyrate, acetate, and propionate have been positively associated with decreasing inflammatory response in cancer [28].

**Gut Microbiota and the Effect on Cancer Therapies**

Gut microbiota is also being explored to determine the relationship between the microbiome environment and the effect of colorectal cancer therapies [44]. One bacterial species previously mentioned as having a potential effect on development of CRC may also enable resistance to chemotherapy used in treatment of CRC [44]. *Fusobacterium nucleatum* enables a cellular recycling process expressed on colorectal cells, making these tumors resistant to chemotherapy-induced cell death [44]. Cancer treatment may promote gut microbiota dysbiosis which may limit therapeutic effectiveness of treatment or it may increase the toxicity of the treatment [45]. Alternatively, treatment may be enhanced by the gut microbiota present in the large intestine, which would improve response to treatment [28]. Therefore, modulating the microenvironment in the colon can vastly influence the outcome of anti-cancer therapies as treatments can modify the individual’s gut.
microbiota and the existing gut microbiota present in the large intestine can affect response to therapies [46].

Immunotherapy

Immunotherapy is a cancer treatment used as a targeted approach in response to carcinoma that aims to both boost the host anti-tumor immune response and addresses cancer resistance and recurrence mechanisms [47]. As the gut microbiome has been shown to influence immune response, emerging studies have also linked microbiome composition with the effectiveness of immune checkpoint inhibitor-based immunotherapy in the treatment of colorectal cancer [48]. The administration of cytosine-guanine dinucleotides (CpG) oligodeoxynucleotides, which are synthetic versions of bacterial DNA, has been shown to stimulate the immune system, presenting an anti-tumor response to some cancers [49]. Also in reference to immunotherapy, the intratumoral injection of this same synthetic version of bacteria administered in conjunction with an anti-interleukin-10 receptor antibody, encourages tumor necrosis factor (TNF) production from tumor infiltrating myeloid cells and initiates a reduction in the growth of several types of tumors, as found in animal studies [50]. Iida N et al. also found in their animal studies that administering *Alistipes shahii*, a specific bacteria, to an antibiotic-treated tumor restored TNF production and improved therapeutic outcome [50]. Research has supported similar findings of implicating commensal gut microbiota in regulating the therapeutic efficacy of immunotherapies [51].

Chemotherapy

Chemotherapy remains one the most common cancer treatments being used in colon cancer [51]. Many of the cytotoxic anticancer therapeutics, including alkylating substances, spindle poisons, platinum and heavy metals, and cytotoxic antimicrobial agents, induce cellular DNA damage and cell division in tumors [51]. Besides the tumor itself, chemotherapy can lead to toxicity in healthy tissues with a high rate of cell division [52]. Gut microbiota plays a role in regulating the response to chemotherapy by immunomodulation, translocation, and enzymatic degradation [51]. Translocation, in particular, deals with the passage of microbiota across the epithelial barrier of the intestine to induce systemic effects of the chemotherapeutic

**Figure 1** Effect of the physiological responses from gut microbiota dysbiosis on risk for colorectal Cancer. Westernized diet may induce bacterial dysbiosis, increase microbial translocation, gut permeability, chronic inflammation, immune responses, and production of carcinogenic toxins, which contribute to the development of colorectal cancer.
agents [53]. Animal studies conducted by Viaud S et al. investigated the role of commensal microbiome in response to chemotherapy treatment exposure and found that the intestinal barrier is disrupted, which promotes translocation of gut microbiota to adjacent lymphatic systems [54]. Gut microbiota has been associated with a direct impact on the pharmacokinetics of chemotherapy medications, the toxicity of these agents, and their impact on tumor activity [55].

Radiotherapy

Radiotherapy, referred to as ionizing radiation therapy, is used in treatment of colon cancer to treat tumors, with immunogenic tumor cell death induced by the genotoxic effect of irradiation [56]. Because of side effects, there are limitations to its use based on safety and effectiveness concerns as health tissues are also damaged by radiation therapy [57]. Side effects can include genomic instability, effects on nearby cells, and systemic treatment-associated immune and inflammatory reactivity [58]. Radiation therapy can alter gut microbiota composition, as well as compromise the intestinal barrier and cause intestinal cell death [57]. While some studies show that gut microbiota composition is changed by radiation therapy, other clinical studies have indicated that introduction of a probiotic can alter the microenvironment during these treatments to enhance outcomes [59,60]. In some clinical studies, probiotics have been shown to help prevent radiation-related enteropathy, specifically formulations containing Streptococcus, Lactobacillus, and Bifidobacterium spp have decreased radiation-induced gut toxicity [59,60]. These findings coupled with existing research offer the potential for clinical practice to include probiotics as adjuvant therapy to help suppress radiation-induced cellular damage [59,60]. We can conclude that gut microbiota, affected by dysbiosis, influences both colorectal cancer pathogenesis and treatment outcomes, as it is involved in regulating the mechanistic response to the cancer as well as the therapeutic interventions [61].

Conclusion

Gut microbiota, modulated by dietary intake, has the potential to affect both development and treatment of colorectal cancer. In light of the prevalence of colorectal cancer in developed and socio-economically stable countries, further research should investigate the strength of the association between the effect of a westernized diet on gut microbiota and the subsequent development of colorectal cancer. Another area of research worthy of further investigation is how gut microbiota influence colorectal cancer in terms of a greater understanding of each species present and the subsequent interaction that may lead to adverse health outcomes. Gut microbiota, being influenced by diet and environmental exposures, should be studied to better understand both the potentially protective effects and also any link to a carcinogenic environment in the colon. Creating a comprehensive microbiome mapping or profiling system would help to identify gut microbiota posing increased risk for formation of cancer development, including the dysbiosis index as developed by Ni J et al. which may help in diagnosis [61]. Understanding how the microbiome is influenced will help to develop strategies to modify gut microbiota to both aid prevention efforts to reduce risk of colorectal cancer and improve therapeutic outcomes for patients undergoing treatment for CRC.

Acknowledgements

This study was funded by the faculty professional development from the College of Health and Human Services at Indiana University of Pennsylvania.

Conflict of Interest

The authors declare no conflict of interest.

References


