Effects of gut microbiome and obesity on the development, progression and prevention of cancer (Review)

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Abstract. Cancer is one of the leading causes of death worldwide and it is estimated that the mortality rate of cancer will increase in the coming years. The etiology of the development and progression of cancer is multifactorial. Insights have been gained on the association between the human microbiome and tumor cell malignancy. A number of commensal microbe species are present in the human gut. They serve pivotal roles in maintaining several health and disease conditions, such as inflammatory bowel disease, irritable bowel syndrome, obesity and diabetes. Known major factors involved in cancer development include age, hormone levels, alcohol consumption, diet, being overweight, obesity, and infections, regardless of the type of cancer. Therefore, the present review aims to discuss the relationship between the gut microbiome and obesity-associated malignancies, including colorectal, gastric and liver cancer. Obesity has been reported to contribute to the development of numerous types of cancer primarily caused by high fatty food intake. In addition, obesity-associated microbiome alterations can lead to cancer and its progression. Dysbiosis of the gut microbiota can alter the metabolite profile, whilst increasing the levels of toxins, such as *Bacteroides fragilis* toxin and colibactin and cytolethal distending toxin, which are responsible for oncogenesis. The present review provides insights into the impact of gut microbiome dysbiosis on the progression of different types of cancers associated with obesity. It also discusses possible strategies for preserving a healthy gut microbiome. Different pre-clinical and clinical models are available for studying cancer development downstream of gut microbiome dysbiosis. Furthermore, the role of metabolites or drugs employed in colorectal, gastric and liver cancer therapy would be discussed.

Contents

1. Introduction

Cancer is a serious public health concern with ~20,000,000 new cases diagnosed and 10,000,000 cases of cancer-related mortality reported worldwide in 2020. According to a World Health Organization (WHO) report, the incidence of cancer is increasing, where it has been predicted that there may be ~28.4 million diagnosed cases worldwide by 2040 (1). Several factors have been reported to contribute to carcinogenesis, although excessive uncontrolled cell division caused by irregular cell signaling is common across most if not all cancer types (2). Hanahan and Weinberg (3) previously proposed six hallmarks of cancer. Specifically, these six hallmarks are resistance to inhibitory growth signals, persistence

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of proliferative signaling, evasion of cell death, initiation of angiogenesis, invasion and metastasis (3). Subsequently, Hanahan and Weinberg (4) added two more details to this six-hallmark concept in 2011, including dysregulation of cell metabolism and circumvention of immune destruction to the critical characteristics of cancer. A decade later, Hanahan (5) then expanded the hallmarks of cancer to include the importance of non-mutational epigenetic reprogramming, phenotype plasticity and the host-microbiome as recent insights in cancer studies emerged. Among these integrative concepts of cancer, the present review aimed to discuss the association between the microbiome and cancer development, in addition to between the microbiome and malignant progression.

The human body contains trillions of symbiotic microbiomes, including a community of bacteria, viruses, fungi and protozoa, which is collectively known as the human microbiota (6,7). Although the skin, oral cavity, respiratory tract and other body parts all harbor microbiomes, the majority of the microbiome population is predominantly contained within the gastrointestinal tract (8). Specifically, the host-associated microbial community within the gastrointestinal system is called the gut microbiome (1). They have been documented to influence various physiological and pathophysiological processes in the body (9). For example, the metabolites produced by an imbalanced microbiota can result in the pathogenesis of certain neurological conditions. Furthermore, physiological energy homeostasis has been reported to be regulated by microbiota, and microbiota-generated butyrate provides energy to colonocytes and prevents autophagy in the colon (9). In addition, microbiota also disrupt physiological homeostasis, host metabolism and contribute to the immune dysregulation (9).

Over the past decade, high-throughput sequencing and multi-omics methods have contributed to the understanding of gut microbiome diversity, elucidating its functional potential (10). Explorative research in the possible relationship between the gut microbiota and various diseases has revealed that alterations in the microbiome profile of the human gut are associated with a number of diseases, including obesity, cancer, diabetes and neurodegenerative diseases (11). However, the causative role mediated by these microbiomes in various disease conditions remains to be fully characterized. This altered population of microbiota has been documented to be great influencers of the host physiology, in processes including digestion, metabolism, cognition and immunity, though additional as yet unrevealed functions are highly likely (12). Several microbiome studies have previously found that other established factors in cancer, including obesity, inflammation and genotoxicity, are either directly or indirectly associated with the interaction between the human microbiota and the human system and metabolism (13,14).

2. Association between obesity and cancer

Obesity is becoming a major global issue and already affects millions of individuals. A person is considered obese when their body mass index (BMI) is >30 kg/m^2. By this metric, ~650,000,000 adults >18 years old are estimated to be clinically obese worldwide, as reported by the WHO (15). Obesity has been reported to associate the incidence of numerous ailments, including type 2 diabetes, hypertension, cardiovascular disease, osteoarthritis, kidney failure, liver inflammation and cancer. In particular, chronic inflammation and altered phenotype due to obesity are the main driving factors in disease progression (16,17).

Previous studies have reported links between cancer and obesity, specifically in terms of the associated mortality rate. Obesity is an important contributing factor to the development of various types of cancer. According to a previous report, ~20% of cancer cases are associated with obesity (18). In addition, obesity enhances colorectal cancer-associated mortality by 14 and 20% in men and women, respectively (19). According to the International Agency for Research on Cancer, obesity is associated with 13 different types of cancer, including breast, colorectal, endometrial, gall bladder, kidney, gastric cardia, ovarian, liver, pancreatic and thyroid cancer, and adenocarcinoma, meningioma and multiple myeloma (20). However, obesity is not the only isolated factor associated with cancer. Age, family history, resident environment, body fat, alcohol, smoking, sex hormone levels, insulin and nutrient levels have all been observed to contribute to cancer development (21).

The excessive deposition of nutrients into the white adipose tissue causes inflammation in obese individuals. Adipocytes in this specialized type of tissue normally functions to store triglycerides as a long-term source of energy in the form of cytoplasmic lipid droplets. White adipose tissues can also secrete various adipokines, including cytokines, hormones and growth factors, which have a role in obesity-associated disease conditions (22,23). These cytokines and growth factors can activate a number of signaling pathways, including NF-κB, JNK and protein kinase R pathways. Low-grade inflammation is induced upon the stimulation of these signaling pathways, which causes the release of common inflammatory cytokines, including IL-1, IL-6 and TNF-α (24). Hyperplasia and hypertrophy of adipocytes can also aggravate this low-grade inflammatory response by increasing the production of free fatty acids, tissue remodeling and changing the profile of adipokine production (25). Furthermore, overproduction of unfolded proteins and subsequent activation of metabolic pathways by endoplasmic stress in obese individuals can activate inflammatory responses (26). Although white adipocyte tissues serve as the primary area for inflammatory pathway activation, other tissues, such as the liver, brain and pancreas, are also associated with obesity-induced inflammation (27). Due to the reported involvement of adipokines in cancer cell growth, the role of leptin and adiponectin in cancer have been widely studied (28,29). It has been reported that low levels of adiponectin may have a permissive role in triggering the neoplastic growth of ERα-positive breast cancer cells through the MAPK-activating signaling pathway (30). Obesity-associated insulin-like growth factor I and insulin resistance are also involved in the stimulation of several types of cancer, according to data produced from previous *in vitro* and *in vivo* analyses (31,32).

According to a previous meta-analysis, malignant melanoma, colon, gallbladder, pancreatic and renal cancer are significantly more common in obese men (33). In obese women, esophageal adenocarcinoma, leukemia, endometrial, colon, gallbladder, pancreatic, postmenopausal breast and renal cancer tended to be more common (Fig. 1). Obese female

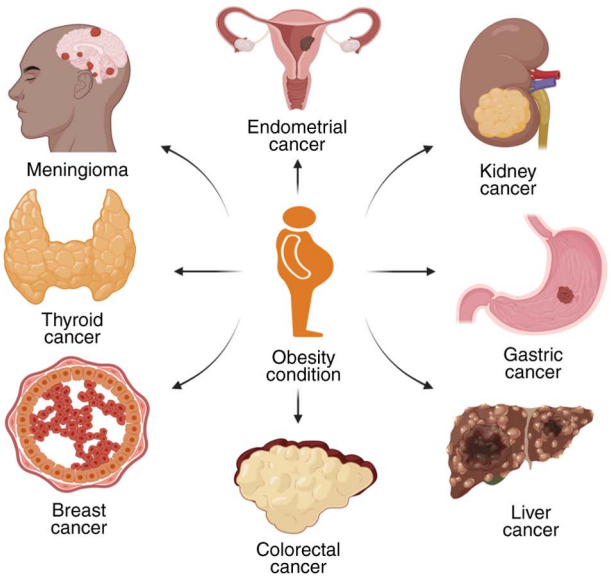

Figure 1. Schematic diagram showing various types of cancer associated with obesity and being overweight.

patients with breast cancer have been reported to show more aggressive characteristics of tumor formation and metastasis (34). In addition, the severity of breast cancer in patients is greatly influenced by age, where women with advancing age are more likely to gain weight and develop obesity. A particularly high risk of breast cancer has been reported in menopausal women between 50 and 60 years old, with weight gain also proposed to be a contributing factor (35). Primary liver cancer is the sixth most common type of cancer globally (36). Several factors have been documented to impact the development of liver cancer. Being overweight is one of the main factors that is associated with the mortality rate of patients with liver cancer and hepatitis viral infection (37,38). Another previous cohort study reported a 17 and 89% liver cancer risk in overweight and obese individuals, respectively, compared with the expected average (39). In addition, this previous study showed that the relative risk of liver cancer for overweight individuals was 1.17 and for obese individuals was 1.89 compared with that in individuals of a healthy weight (39). Liver cancer associated with obesity or excess body weight was reported to be more prevalent in men compared with women, with individuals with excess body weight suffering from liver cirrhosis or hepatitis C viral infection being more prevalent (40).

The increased incidence and prevalence of obesity among populations have elevated the risk of gastrointestinal cancer development. It has been suggested that excess adiposity is a potential cause of gastrointestinal tract, pancreatic, colorectal, esophageal, stomach and gallbladder cancer. The relationship between obesity and gastrointestinal cancer has been proposed to be associated with changes in insulin and insulin-like growth factor I signaling, altered sex hormone metabolism and chronic low-grade inflammation (41). Previous studies have indicated a strong connection between overall fat content and elevated gastro-esophageal reflux, Barrett's esophagus and esophageal adenocarcinoma (42,43). Although reflux can be adjusted in obese individuals, rates of esophageal adenocarcinoma have been shown to be more prevalent whereas waist circumference (a measure of obesity) is associated with the high occurrence of Barrett's esophagus (44). The importance of obesity (specifically central obesity) as a predisposing factor for colorectal cancer, which is the third most common cause of global cancer mortality, has been frequently reported (45,46). The increased deposition of abdominal fat and associated obesity is highly associated with the prevalence of colorectal cancer (47).

3. Mechanistic role of bacteria in carcinogenesis

The human gut is inhabited by a diverse microbiome, which forms a complex community along the gastrointestinal tract and contributes to the health and well-being of the host. Although it is well-known that these microbiomes interact and maintain a status of symbiosis with the host, alterations in the microbial flora can adversely affect biological functions in the body (4). A recent study by Hou *et al* (48) on the role of the human microbiota reported the dynamic role of the gut microbiota in host health and its relation to pathogenesis of cancer. The gut microbiome can influence the systemic functioning of the body through the gut-brain axis, colonization resistance and immunomodulation (48). In addition, the strong influence of the human gut microbiota in developing various ailments, including cancer, respiratory, neurophysiological, hepatic and kidney diseases, has been previously reported (Table I).

Cancer is caused by a multitude of factors, including both genome modulation and environmental causes. However, the association between the human microbiota and cancer development has not been considered until the 1990s. Microbiome involvement in carcinogenesis was first detected in gastric cancer in 1994, resulting in the subsequent recognition of *Helicobacter pylori* as a group 1 carcinogen by the WHO (49,50). The role of the human microbiota in several types of cancer has since been reported, including oral squamous cell carcinoma (51,52), lung cancer (53), breast cancer (54) and genitourinary cancer (55). Several mechanisms contributing to cancer development have been observed to be mediated by the gut microbiome, including the production of microbiota-derived metabolites, immune dysregulation and the modification of genetic and epigenetic factors (56). Previous studies have demonstrated that the intracellular bacteria *Chlamydia psittaci* can cause ocular adnexal lymphoma by regulating oxidative DNA damage and modulating the NF-κB pathway connected with anti-apoptotic effects (57,58). In addition, the non-motile gram-negative bacteria *Porphyromonas gingivalis* has been shown to be associated with oral cancer through the epithelial-mesenchymal transition of oral epithelial cells and by inducing MMP-9 and IL-8 expression (59). The pathogenic *Mycobacterium tuberculosis* can also promote lung cancer development and metastasis by modulating the T-cell immune response by elevating the activity of the programmed cell death protein-1/programmed death-ligand 1 pathway (60). In addition, the intracellular pathogen *Chlamydia pneumoniae* can promote lung cancer through by provoking the monocytes into secreting TNF-α, IL-8 and superoxide radicals, which promote cellular and DNA damage (61). The gram-negative bacteria *Salmonella typhi* leads to gallbladder cancer through typhoid toxin-mediated alteration of the cell cycle and DNA damage (62). Other non-motile

Table I. Mechanistic role of microbes in carcinogenesis.

Microbe	Associated cancer	Key mechanisms	(Refs.)
Porphyromonas gingivalis	Oral cancer	The epithelial-mesenchymal conversion of oral epithelial cells, inducing MMP-9 and IL-8	(59)
Chlamydia psittaci	Ocular adnexal lymphoma	Regulating oxidative DNA damage and modulating the NF-κB pathway connected with anti-apoptotic effects	(57)
Mycobacterium tuberculosis	Lung cancer	Modulating T-cell immune response by elevating expression of the programmed cell death protein-1/programmed death-ligand 1 pathway	(60)
Chlamydia pneumoniae	Lung cancer	Triggering monocytes to secrete TNF, IL-8 and superoxide radicals, which promote cellular and DNA damage	(61)
Salmonella typhi	Gallbladder cancer	Typhoid toxin-mediated alteration of cell cycle and DNA damage	(62)
Streptococcus bovis/ *Streptococcus gallolyticus*	Colorectal cancer	Degrading anticancer substances, including tannic acid, and triggering inflammatory cytokines, including TNF-α, IL-1β, IL-6 and IL-8, to cause free radical formation, which results in DNA alteration and leads to cancer condition	(63)
Parabacteroides	Colorectal cancer	Antagonize the toll-like receptor 4 and AKT signaling pathways, which lead to cancer development and progression	(125)
Helicobacter pylori	Gastric cancer	Increase accumulation of inflammatory cytokines including IFN-γ, IL-1, IL-6, IL-7, IL-8, IL-10, IL-18 and TNF-α, and stimulate diverse ranges of immune cells, including lymphocytes, eosinophils, macrophages, mast cells and neutrophils	(49,50)

gram-positive bacteria, including *Streptococcus bovis* and *Streptococcus gallolyticus*, have also been documented to contribute to colorectal cancer by degrading anticancer substances, including tannic acid (63). Furthermore, bacteria can trigger the release of inflammatory cytokines, including TNF-α, IL-1β, IL-6 and IL-8, to cause free radical formation, resulting in DNA alterations and cancer (64).

Over the last two decades, there has been an increase in studies investigating the impact of the gut microbiota on cancer. However, the fundamental cause of gut microbiota-induced tumor initiation remains unknown, meaning that it cannot yet be exploited for the treatment of cancer. A number of different hypotheses regarding the impact of the microbiota on cancer prognosis and therapy have been proposed. Microbial metabolites can interrupt cell signaling pathways involved in various processes, such as cell proliferation, division, programmed cell death and interaction with cell from other organs (65). It is also well-known that inflammatory conditions can significantly increase the risk of cancer, representing a pivotal hallmark of the complex process of carcinogenesis. Previous studies have revealed that enteric bacteria can significantly impact the immune system, serving a crucial role in the development of local and systemic inflammation (66,67). Notably, the gut microbiome can inhibit infection by adjusting the niche environment and regulating host immune defense (68). The interaction between cancer cells and other cell types, such as immune cells, myeloid cells and cancer-associated fibroblasts, forms the tumor microenvironment (TME) (69). It is important to note that there is accumulating evidence suggesting an essential link among gut microbiome changes, inflammation and cancer development, in a complex and multifaceted mechanism. High-throughput sequencing has revealed that aspects of bacterial niches can be detected in TME of various types of cancer, which may influence the development of cancer by modulating the immune system (65,68). The mechanistic role of microbes in carcinogenesis is detailed in Table I. In a recent review on the TME in various types of cancer, Chen *et al* (70) reported that the microbiota tended to differ between cancer and normal tissues (70). A previous comparative case study of gut microbial diversity and composition involving healthy individuals and patients with colon cancer through 16S rDNA sequencing revealed that the levels of beneficial bacteria were decreased, whilst the levels of several harmful bacteria were increased, in the cancer group (71). In another review of the interaction between the microbiota and the immune system, it was described that alterations in the gut microbiome can significantly impact the immune system and related signaling mechanisms through direct cell interaction or microbiota-derived metabolites (72).

Previous studies on the interaction between the gut microbiome and immunity has revealed that the gut microbiome can participate in immune modulation and can promote liver cancer through bile acid metabolism (73,74). Furthermore, assessing the role of microbial metabolites in immune regulation revealed that some of these small to large macromolecules can modulate cell signaling pathways that evoke a positive or negative response in cells (72). Polyamine derivatives found in the microbial metabolites have been reported to activate the *Myc*

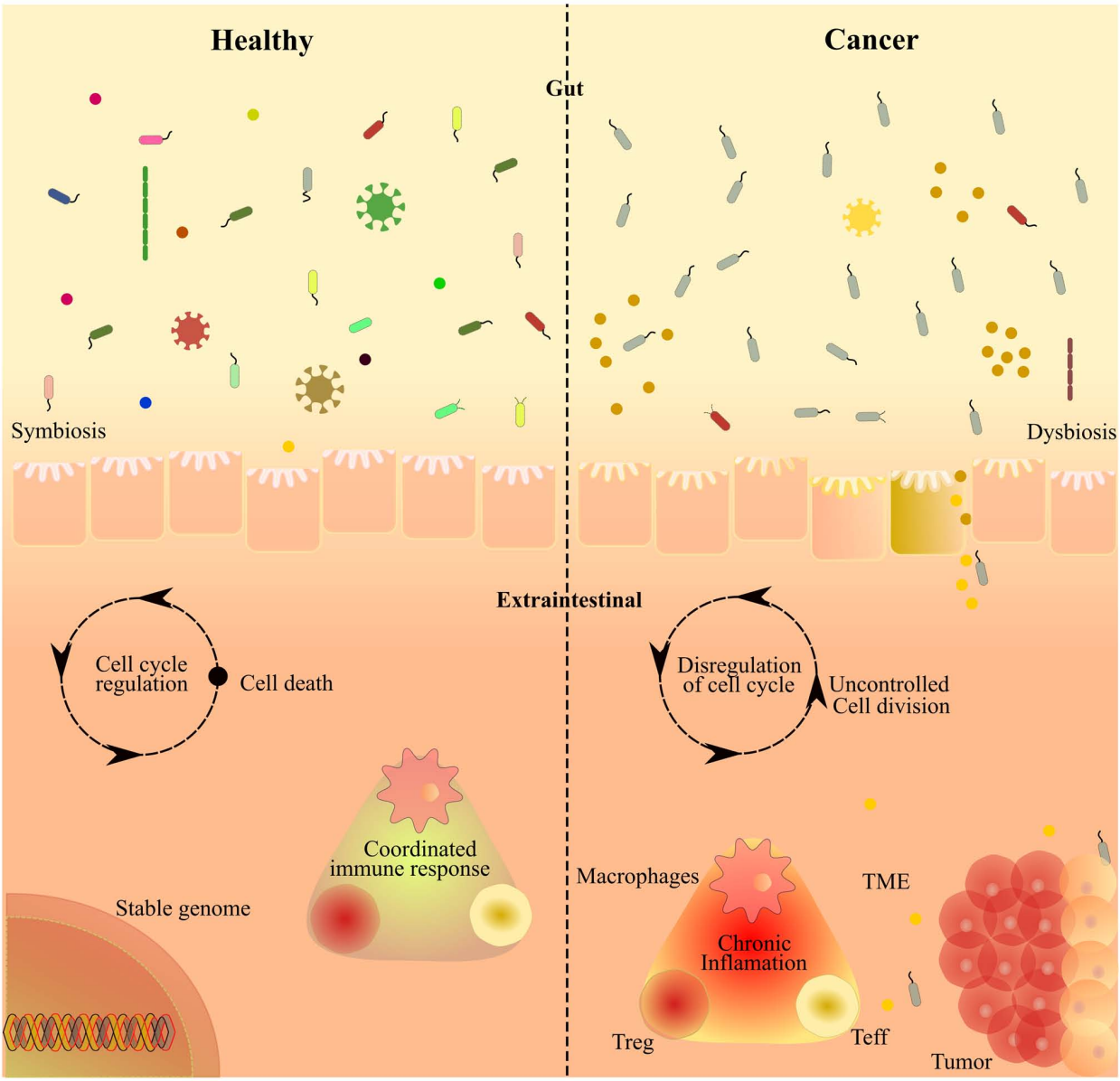

Figure 2. An illustrative representation of the intricate relationship between the gut microbiome, cellular processes and cancer progression. The left side of the illustration depicts a healthy symbiotic condition, characterized by its diversity, with various microbial species maintaining a balanced relationship with the host. By contrast, on the right side, the illustration focuses on an inflamed condition, showing altered microbiota composition and its impact on the cellular processes, resulting in uncontrolled cell division through cell cycle dysregulation. In this state, the microbial diversity is decreased, which causes an imbalance in the microbiota. This type of dysbiosis leads to disruption of the gut barrier, allowing the translocation of microbial components and inflammatory molecules into the bloodstream and nearby cells. It is proposed that a dysbiotic microbiome enhances inflammation, promoting tumor growth and metastasis. TME, tumor microenvironment; Treg, regulatory T cell; Teff, effector T cell.

oncogene, promoting cancer progression. The *c-Myc* class of transcription factors are crucial for controlling the expression of genes involved in cell growth, proliferation and differentiation. In addition, butyrate derivatives have been demonstrated to exhibit antitumor proprieties, inhibiting inflammation and carcinogenesis by regulating *Wnt* and *NF-κB* signaling pathways (75). The interplay among gut microbiota, inflammation and immune responses can also affect the systemic immune response. These aforementioned observations suggest that the gut microbiome and its metabolites can significantly impact various biological processes, such as cell metabolism and immune regulation, and thus affect health (Fig. 2). Fig. 2 illustrates the intricate interplay between the gut microbiome, cellular processes and cancer progression.

4. Gut microbiome, obesity and gastric cancer

According to the GLOBOCAN database, gastric cancer is the fourth leading cause of cancer-related mortality worldwide (1,76). Gastric cancer is particularly prevalent in developing countries, with a two-fold higher incidence rate in men compared with that in women (74). Several epidemiological studies have highlighted the robust association between obesity and gastric cancer. In a previous meta-analysis, Lin *et al* identified an association between increased BMI and gastric cancer. In addition, obesity (BMI, ≥30 kg/m^2) was found to be associated with an increased risk of gastric cancer compared with being overweight (BMI, 25.1-30 kg/m^2) and normal weight (BMI, 18.5-25 kg/m^2) (77).

In 2014, Donohoe *et al* demonstrated the inter-relationship between adipose and the TME in gastric cancer (44). Specifically, inflammation, hypoxia, energy metabolism and angiogenesis were all found to be key factors associating obesity with gastric cancer, which are commonly dysregulated in the TME and adipose tissue Karczewski *et al* (41) previously demonstrated that the primary pathophysiological mechanisms connecting obesity and gastric cancer include altered levels of insulin signaling, chronic low-grade inflammation in the adipose tissue and altered steroid hormone production and metabolism. Lee *et al* (78), in a Health Examinees-Gem study, reported that obesity during early adulthood (20-39 years) was significantly associated with an increased risk of gastric cancer.

The interaction between microorganisms and tumors has garnered widespread attention, with the aim of delineating the features of the complex microbial communities and their possible role in carcinogenesis (13). Numerous studies have discussed the connection between gut microbes and low-grade inflammation, which can regulate the innate and adaptive immune responses, at least in part contributing to the initiation and progression of oncogenic conditions (5,79).

H. pylori-mediated infection can stimulate immune responses and inflammation to regulate gastric cancer (80). The immune response of epithelial and myeloid cells to *H. pylori* bacteria is regulated by the gastric microbiota, which in turn determines the outcome of the disease. The contact between *H. pylori* and gastric epithelial and myeloid cells has been shown to induce signaling through innate pathways, leading to changes in cellular homeostasis, and the release of cytokines and chemokines that can trigger the inflammatory responses. *H. pylori* infection disturbs the balance between the host gastric microbiota and mucosa-related factors leading to inflammatory changes, dysbiosis and subsequently gastric cancer (81). *H. pylori* is a group 1 carcinogen that can promote gastric carcinogenesis by aggravating inflammation in the gastric mucosa (81,82). The key virulence factors of *H. pylori*, namely cytotoxin-associated gene (Cag)A and vacuolating toxin A (VacA), are associated with an increased risk of gastric cancer (13,83). Infection with the *H. pylori* CagA strain results in an increased accumulation of inflammatory cytokines, including *IFN-γ*, *IL-1*, *IL-6*, *IL-7*, *IL-8*, *IL-10*, *IL-18* and *TNF-α*, which stimulates a diverse range of immune cells, including peripheral mononuclear cells, lymphocytes, eosinophils, macrophages, neutrophils and mast cells (13,84). In addition, infection with the Cag^+ strain leads to the upregulation of the *ERK/MAPK, PI3K/AKT, NF-κB, Wnt/β-Catenin*, Sonic Hedgehog and *STAT3* signaling pathways, whilst downregulating the activity of tumor suppressor pathways (74,85).

The *VacA* virulence factor leads to cellular vacuolation and autophagy in human gastric epithelial cells (86,87). *VacA* has been reported to upregulate *MAPK, ERK1/2* and vascular endothelial growth factor expression, whilst also stimulating the Wnt/β-catenin signaling pathway, which is required for cell proliferation and differentiation (88,89). Simultaneously, *H. pylori* infection can also induce methylation in genes expressing the cell adhesion glycoprotein E-cadherin and various tumor suppressors, such as trefoil factor 2 and fork-head box transcriptional regulator D3, leading to the increased risk of gastric adenocarcinoma (90-92).

Advancements in sequencing technology have improved the understanding into the complexity of the gastric microbiota (13,93). *H. pylori*-negative individuals harbor distinct microbial populations, including Proteobacteria, Firmicutes and Actinobacteria (94,95). Sequencing-based and quantitative PCR approaches have confirmed that patients with gastric cancer tended to harbor a diverse population of microbiota with a reduced level of *Porphyromonas*, *Neisseria*, TM7 group and *Streptococcus sinensis*, but an enriched level of *Klebsiella pneumoniae*, *Lactobacillus coleohominis* and Lachnospiraceae (95,96). The pathogenic components, including the outer-membrane, nickel-binding and BAK proteins of non-*H. pylori* microbiota, including *Helicobacter cinaedi*, *Lactobacillus coleohominis* and *Klebsiella pneumoniae*, assist their colonization on the gastric mucosal layer, leading to tumorigenesis in the stomach (97).

A high-fat diet large quantities of fatty acids and low amount of vitamins, fibers and minerals are considered the primary cause of obesity (98). Several studies have demonstrated that a high-fat diet can promote gastric cancer through metabolic reprogramming and alteration of intestinal microbes. Arita and Inagaki-Ohara (99) reported that a high-fat diet can increase leptin signaling and promote gastric microbial dysbiosis, leading to intestinal metaplasia. In addition, this previous study found that a high-fat diet given to mice elevated *Lactobacillus* levels and reduced *Bifidobacteria* levels. *Lactobacillus* is a homofermentative probiotic bacterium that converts lactose to lactic acid. Lactic acid is associated with gastric carcinogenesis as it regulates inflammation, metastasis and epithelial-mesenchymal transition (100).

He *et al* (101) found that 12 weeks of a high-fat diet feeding in C57BL/6 mice resulted in dysbiosis of the gastric microbiota, with a reduced level of community diversity. This high-fat diet also increased the levels of Proteobacteria and Firmicutes, whilst downregulating those of Bacteroidetes and Verrucomicrobiota. Furthermore, enriched levels of Enterobacteriaceae were detected, which are associated with increased plasma and fecal endotoxin production. Endotoxin is known to trigger chronic inflammation and can induce obesity (102). Previously, Xiao *et al* (103) reported that endotoxin-producing opportunistic pathogens, such as Enterobacteriaceae and Desulfovibrionaceae, can produce lipopolysaccharide (LPS) and lead to metabolic endotoxemia. LPS can enhance C-X-C chemokine receptor type 7 expression in gastric cancer, subsequently regulating the proliferation and migration of gastric cancer cells through the toll-like receptor 4 (TLR4)/myeloid differentiation factor 2 signaling pathway (104). Furthermore, Desulfovibrionaceae can reduce sulfate to hydrogen sulfide (H_2S) (105). H_2S then activates the fatty acid receptor CD36 in gastric cancer cells to stimulate lipid metabolic reprogramming and gastric cancer metastasis (7).

5. Gut microbiome, obesity and colorectal cancer

Colorectal cancer is the third most common cancer diagnosed worldwide, with incidence rates 30% higher in men compared with those in women (2). Several epidemiological studies have demonstrated the relationship between obesity and colorectal

Table II. Association between obesity, microbiome alteration and carcinogenesis.

Obesity condition	Changes in gut microbiome level	Associated cancer	Mechanism	(Refs.)
High-fat diet associated with obesity	Upregulation of *Lactobacillus* and downregulation of *Bifidobacteria*	Gastric cancer	*Lactobacillus* converts lactose to lactic acid, which acts as a major source of gastric carcinogenesis	(98)
	Enriched levels of *Enterobacteriaceae* and *Desulfovibrionaceae*	Gastric cancer	Endotoxin-producing opportunistic pathogens produce lipopolysaccharide, which enhances C-X-C motif chemokine receptor R7 expression and promotes migration of gastric cancer cells	(102,103)
	Upregulated levels of *Desulfovibrionaceae*	Gastric cancer	The bacteria reduce sulfate to hydrogen sulfide, which induces fatty acid receptor CD36 in gastric cancer cells	(104, 105)
Western diet-associated obesity	Enhances the level of collagenase-producing microbes	Colorectal cancer	Colonization of collagenase-producing microbes leads to the transmigration of colorectal cancer cells and results in recurrence	(122)
	Upregulated levels of *Clostridium*	Colorectal cancer	*Clostridium* converts the primary bile acids to secondary bile acids. Excessive accumulation of bile acids leads to the development of colorectal cancer	(124)
Western diet and high-fat diet-associated obesity	Abundance of *Parabacteroides* in intestine	Colorectal cancer	Antagonizes the toll-like receptor 4 and AKT signaling pathways, which leads to colorectal cancer development and progression	(125)
	Enrichment of pro-inflammatory pathogens and reduction of butyrate-producing gut microbes	Colorectal cancer	Results in dysbiosis and leads to tumor formation through enhanced levels of the microbial metabolite trimethylamine *N*-oxide, the pro-inflammatory cytokine IL-1β and the intestinal permeability marker Zonulin, and reduced levels of the anti-inflammatory factor IL-10	(120)
Obesity with non-alcoholic fatty liver	Increased levels of liver proteobacteria	Liver cancer	Causes gut dysbiosis, which promotes hepatocellular carcinoma	(131)
Dietary obesity	Enhanced levels of gram-positive intestinal microbiota	Liver cancer	Increases the levels of gut bacterial metabolite deoxycholic acid, which causes DNA damage and induces liver carcinoma	(132)

cancer. Bardou *et al* (106) reported that obesity is associated with 11% colorectal cancer cases in the European population. Among the list of obesity conditions, visceral fat and abdominal obesity are associated with a higher risk of colorectal cancer compared with subcutaneous obesity. It has also been previously reported that obese individuals exhibit a 20-40% higher risk of colorectal cancer compared with normal-weight individuals (107,108).

Obesity leads to colorectal cancer development through inflammation, metabolic regulation and signaling processes (109). In a meta-analysis on the relationship between BMI and colorectal cancer, Ma *et al* (110) reported the relevant risk of colorectal cancer to be 1.334 (95% CI, 1.253-1.420) for obese individuals compared with individuals of a healthy weight. In a pooled analysis of eight population-based cohort studies, Matsuo *et al* (111) also revealed a strong association between obesity and colorectal cancer. The association was stronger in men compared with that in women, with the association higher in the proximal colon compared with the rectum. Recently, Socol *et al* (112) demonstrated that genetic variation and aberrant signaling in the leptin pathway were associated with obesity and colorectal cancer. Leptin receptor (*LEPR*) expression is critical for the proliferation of colorectal carcinoma cells (Table II). Higher expression of *LEPR* has been shown to lead to neoangiogenesis and increased metastatic potential of colorectal carcinoma. By contrast, a lack of *LEPR* expression reduces tumor proliferation in colorectal carcinoma (113).

A high-fat diet has been shown to promote colorectal cancer progression and metastasis. Niku *et al* (114) previously demonstrated that a Western diet, containing high fat and low fiber, calcium, vitamin D and folate, acts as a risk factor for the development of colorectal adenoma, through the heterozygous loss of adenomatous polyposis coli and overactivation of the AKT, mTOR and ERK1/2 signaling pathways in C57BL/6 J Min/+ mice. Park *et al* (115) demonstrated in another study that high-fat diet-related obesity can lead to inflammation-associated colorectal cancer by activating the PI3K/AKT signaling pathway and triggering the expression of IL-12, monocyte chemoattractant protein-1 and TNF-α in the TME.

Several studies have highlighted the altered gut microbiota signatures in colorectal cancer development (6,7). The lower population of the butyrate-producing *Clostridium* cluster IV and XIV bacteria has previously been associated with colorectal cancer (116). Besides, the population of Firmicutes, Actinobacteria and Lachnospiraceae have also been reported to be increased in pre-malignant colorectal adenoma, whereas Proteobacteria, Enterobacteriaceae and *Sutterella* species have been shown to be increased during colorectal cancer progression (117). Apart from the bacterial population, temperate phages have also been associated with the development of colorectal cancer. The bacteriophages interact with the host bacteria and stimulate the progression of colorectal cancer by changing the bacterial community structure and regulating the immune microenvironment (118).

Intestinal microbes can regulate polyamine synthesis, LPS production, butyrate metabolism and oxidative phosphorylation to facilitate the occurrence and development of colorectal cancer (119,120). Schulz *et al* (121) reported that a high-fat diet can lead to small intestinal tumor formation in *K-ras*^{G12Dint} mice by altering the composition of intestinal microbes. Gaines *et al* showed that a Western pattern diet can enhance the levels of collagenase-producing microbes, including *Proteus mirabilis*, *Candida parapsilosis* and *Enterococcus faecalis*, in the intestine of the BALB/c mice (122). Colonization by these microbes leads to the transmigration of colorectal cancer cells and promotes colorectal cancer recurrence. Furthermore, the intestinal microbes in obesity can enhance bile acid secretion in the intestine (123). The gram-positive *Clostridium* converts primary bile acids to secondary bile acids, where the excessive accumulation of secondary bile acids can lead to colorectal cancer (124). In addition, high-fat diet- and Western diet-mediated obesity can reduce the abundance of Parabacteroides in the intestine. Parabacteroides antagonize the TLR4 and AKT signaling pathways (125), which are upregulated during colorectal cancer development and progression. Therefore, antagonizing *Parabacteroides* in the intestine through high-fat diet-related obesity can promote colorectal cancer. Sánchez-Alcoholado *et al* demonstrated that obese patients with colorectal cancer exhibit a reduced population of butyrate-producing gut microbes, including *Butyricimonas*, *Roseburia*, *Faecalibacterium* and *Ruminococcus*, with an abundance of opportunistic pathogens, including *Fusobacterium*, *Desulfovibrio*, *Clostridium* and *Enterococcus* (120). The enrichment of these proinflammatory pathogens and reduction in butyrate-producing bacteria results in dysbiosis and leads to tumor formation, through elevated levels of the deleterious microbial metabolite trimethylamine *N*-oxide, the proinflammatory cytokine *IL-1β* and the intestinal permeability marker Zonulin, in addition to the reduced levels of the anti-inflammatory factor *IL-10*.

6. Gut microbiome and liver cancer

Obesity and high-fat-content food are closely associated with the progression of liver cancer. Liver cancer progression is associated with the modified gut microbiome. Previous reports have explored the involvement of the gut microbiome in chronic liver disease and liver cancer (126,127). Liver inflammation causes changes in the gut microbiome, causing microbiome dysbiosis and variations in the intestinal barrier, resulting in a leaky gut (128). In the majority of cases, liver cirrhosis leads to leakiness and dysbiosis, whilst increasing the risk of liver cancer. Patients with liver cirrhosis can also exhibit sudden bacterial peritonitis, contributing to hepatocellular carcinoma (129). Fatty liver disease is also associated with liver carcinoma, even in non-alcoholic patients without cirrhosis (130). Intestinal microbiome dysbiosis in non-alcoholic patients has also been characterized in the pathogenesis of fatty liver disease (130).

Inflammatory bowel disease, type 1 diabetes, autism, cardiovascular diseases, and obesity favor gut microbiome alterations. Gut metabolites produced during gut dysbiosis induced by obesity in the enterohepatic circulation have been reported to promote hepatocellular carcinoma (7,131). A previous study reported that circulation of deoxycholic acid triggers the senescence-associated secretory phenotype in hepatic stellate cells (HSCs), which can result in the secretion of several tumor-promoting factors in the liver of C57BL/6 mice (131,132). The gut microflora-derived bacterial products, such as LPS and bacterial DNA, and endogenous substances, including free fatty acids, trigger the activation of hepatic TLR4, which leads to liver inflammation, fibrosis and cancer (132).

In a previous microbiome analysis of patients and healthy individuals, patients with carcinoma induced by hepatitis B were reported to possess an abundance of *Escherichia*, *Shigella* and *Enterococcus*, whereas decreased levels of *Faecalibacterium*, Ruminococcus, *Ruminoclostridium* sp. *Clostridium*, *Corynebacterium*, *Bacillus*, *Desulfovibrio* and *Rhodococcus* sp. were observed in non-alcoholic patients with steatohepatitis-associated hepatocellular carcinoma. By contrast, in patients with cirrhosis-related carcinoma, higher levels of Epsilonproteobacteria, Actinobacteria, Clostridia, *Fusobacterium* and *Oribacterium* were observed compared with in healthy volunteers (133).

7. Gut microbiota interventions in cancer: Pre-clinical and clinical studies

Data from model systems, such as rodents, coupled with those from robust clinical trials, have provided evidence on the role of the gut microbiome in the progression of obesity-associated cancer, where insights have been gained on potential therapeutic interventions. Previous pre-clinical and clinical trials have studied the effect of microbial inflammation on the development of the pathophysiology of different types of

cancer (14,134). Several pre-biotics have shown anticancer properties against colorectal cancer models. Prenyl flavonoids have been reported to improve the gut microbiome in *in vitro* models of colorectal cancer and to exert anticancer activity (134). In addition, a high-fat diet (HFD) is known to induce gut dysbiosis. The oral intake of agaro-oligosaccharides (AGO) has been shown to prevent HFD-mediated gut dysbiosis and to thus inhibit colon carcinogenesis in C57BL/6N mice. This previous study reported that phospholipids and bile acids were downregulation in C57BL/6N mice receiving a HFD alone, whereas this downregulation was recovered with the administration of AGO supplements (135). A double-blind crossover study involving healthy human adult volunteers (n=31) reported that polydextrose (PDX) can modulate the composition and function of the colonic microbiota. Besides, PDX was found to be associated with the change in microbial metabolism, including production of butyrate and reduction in metabolic byproducts of bacterial putrefaction including branched-chain fatty acids. This previous study demonstrated that PDX significant reduced the fecal water genotoxicity of volunteers after consumption, thus indicating the potential of PDX for reducing the risk factors associated with colorectal cancer (136). Fermentation of sugar in the colon tends to favor butyrate-producing bacteria, Ruminococcus and *Clostridium* clusters I, II and IV (136). Administration of the antibiotic cefoxitin in a murine model has been shown to reduce enterotoxigenic *Bacteroides fragilis*-driven inflammation and colon cancer (13,137). In addition, short-chain fatty acids favor the restoration of intestinal health and the gut microbiome to prevent colon cancer. Several mice and human studies have demonstrated the role of short-chain fatty acid-synthesizing bacteria in the treatment and prevention of cancer (138,139).

In a mouse model, altered intestinal microbiota can in turn alter antitumor immune surveillance, which can increase the risk of liver disease and therefore cancer development. $NEMO^{\Delta EMOc}/Nlrp6^{-/-}$ mice exhibited the hallmarks of intestinal dysbiosis, as well as aggravated steatohepatitis and increased tumor burden. A significant finding of this previous study was that the loss of intestinal *Akkermansia muciniphila* could increase the abundance of hepatic monocytic myeloid-derived suppressor cells and T cells associated with the proliferation and expansion of liver cancer cells (140). Understanding the gut-liver axis and microbiome involvement in liver carcinoma development may facilitate the design of effective therapeutic methods. Data from rodent models and clinical trials have suggested using the gut-liver axis as a target for inhibiting liver cancer but not for the complete treatment. Several drugs, such as antibiotics, probiotics, TLR4 antagonists and prokinetics, have been shown to control non-cancerous liver disease and carcinoma progression in rodent models and human patients (141). In a previous retrospective study, patients with liver cirrhosis who received rifaximin exhibited a reduced risk of liver carcinoma development (142). In another study involving patients with liver cirrhosis, administration of different antibiotics and probiotics was found to reduce the development of primary hepatocellular carcinoma and mortality (143). Fecal microbiota transplantation (FMT) is one of the methods used to modulate the gut microbiota and reverse dysbiosis. During this process, a new bacterial population is transferred to the recipient to reverse the dysbiosis that occurred. Microbial species equilibrium is maintained in the gut by introducing fecal transplants from healthy individuals (140). FMT has been reported to improve survival in patients with metastatic gastro-esophageal cancer studied in randomized, double-blind, placebo-controlled pilot trials (143,144). By contrast, the transfer of allogenic FMT from an obese donor to a lean recipient can induce the obese phenotype and its associated metabolic dysfunctions in the lean recipient (145). Another study previously revealed the effectiveness of FMT along with anti-programmed cell death protein 1 in six out of 15 patients with melanoma (146). Several mouse model studies and clinical trials have provided information on FMT and its ability to reverse the intestinal dysbiosis, relieve colon and hepatocellular carcinoma symptoms, whilst facilitating their management (147,148).

8. Future directions and conclusions

The Gut microbiota aids in the homeostasis of health and disease. The commensal gut microbiome helps to maintain homeostasis by producing beneficial metabolites. However, under the conditions of altered microbiomes induced by various factors, it can promote carcinogenesis. The present review discussed the close association between gut microbes and gastric, colorectal and liver cancer, whilst also discussing potential prevention strategies. It has been observed that microbiome dysbiosis leads to alterations in the profile of essential metabolites, which in turn causes the production of toxins. These metabolites enhance inflammation in the host and can lead to the formation of tumors. Obesity has been reported to serve as a factor associated with the initiation and progression of 13 types of cancer. Therefore, exploring and employing appropriate microbes or microbial-derived molecules is recommended to develop a beneficial gut microbiota that can elicit appropriate immune responses against cancer cells. Probiotics and other cancer therapies are recommended for re-establishing gut microbiota and producing an anti-tumorigenesis environment. In the future, more personalized trials or approaches are sorted to verify the effects of probiotics on different types of cancer by modulating the microbiome.

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Availability of data and materials

Not applicable.

Authors' contributions

RK designed the study. HP, SP, and VA prepared the figures. RK, HP, SP, and VA wrote the manuscript. RK, SB, SP, and

MD critically revised the manuscript. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

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Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Deo SVS, Sharma J and Kumar S: GLOBOCAN 2020 report on global cancer burden: Challenges and opportunities for surgical oncologists. Ann Surg Oncol 29: 6497-6500, 2022.
2. Siegel RL, Wagle NS, Cercek A, Smith RA and Jemal A: Colorectal cancer statistics, 2023. CA Cancer J Clin 73: 233-254, 2023.
3. Hanahan D and Weinberg RA: The hallmarks of cancer. Cell 100: 57-70, 2000.
4. Hanahan D and Weinberg RA: Hallmarks of cancer: The next generation. Cell 144: 646-674, 2011.
5. Hanahan D: Hallmarks of cancer: New dimensions. Cancer Discov 12: 31-46, 2022.
6. Ursell LK, Metcalf JL, Parfrey LW and Knight R: Defining the human microbiome. Nutr Rev 70: S38-S44, 2012.
7. Wang R, Tang R, Li B, Ma X, Schnabl B and Tilg H: Gut microbiome, liver immunology, and liver diseases. Cell Mol Immunol 18: 4-17, 2021.
8. Dekaboruah E, Suryavanshi MV, Chettri D and Verma AK: Human microbiome: An academic update on human body site specific surveillance and its possible role. Arch Microbiol 8: 2147-2167, 2020.
9. Kuźniar A, Szawica D, Wąsiewicz E, Fularska K and Oleszko M: Human gut microbiome-how intestinal bacteria influence our health. J Educ Health Sport 1: 30-35, 2023.
10. Zhu X, Li B, Lou P, Dai T, Chen Y, Zhuge A, Yuan Y and Li L: The relationship between the gut microbiome and neurodegenerative diseases. Neurosci Bull 37: 1510-1522, 2021.
11. Hoesel B and Schmid JA: The complexity of NF-κB signaling in inflammation and cancer. Mol Cancer 12: 1-15, 2013.
12. Guinane CM and Cotter PD: Role of the gut microbiota in health and chronic gastrointestinal disease: Understanding a hidden metabolic organ. Ther Adv Gastroenterol 4: 295-308, 2013.
13. Meng C, Bai C, Brown TD, Hood LE and Tian Q: Human gut microbiota and gastrointestinal cancer. Genomics Proteomics Bioinformatics 16: 33-49, 2018.
14. Bhatt AP, Redinbo MR and Bultman SJ: The role of the microbiome in cancer development and therapy. CA Cancer J Clin 67: 326-344, 2017.
15. Boutari C and Mantzoros CS: A 2022 update on the epidemiology of obesity and a call to action: As its twin COVID-19 pandemic appears to be receding, the obesity and dysmetabolism pandemic continues to rage on. Metabolism 133: 155217, 2022.
16. Calle EE, Rodriguez C, Walker-Thurmond K and Thun MJ: Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S adults. N Engl J Med 17: 1625-1638, 2003.
17. Martin-Rodriguez E, Guillen-Grima F, Martí A and Brugos-Larumbe A: Comorbidity associated with obesity in a large population: The APNA study. Obes Res Clin Pract 5: 435-447, 2003.
18. Wolin KY, Carson K and Colditz GA: Obesity and cancer. Oncologist 6: 556-565, 2010.
19. Amersi F, Agustin M and Ko CY: Colorectal cancer: Epidemiology, risk factors, and health services. Clin Colon Rectal Surg 3: 133-140, 2005.
20. Lauby-Secretan B, Scoccianti C, Loomis D, Grosse Y, Bianchini F and Straif K: Body fatness and cancer-viewpoint of the IARC working group. N Engl J Med 8: 794-798, 2016.
21. Deslypere JP: Obesity and cancer. Metabolism 44: 24-27, 1995.
22. Fasshauer M and Blüher M: Adipokines in health and disease. Trends Pharmacol Sci 7: 461-470, 2015.
23. Gregor MF and Hotamisligil GS: Inflammatory mechanisms in obesity. Annu Rev Immunol 29: 415-445, 2011.
24. Longo M, Zatterale F, Naderi J, Parrillo L, Formisano P, Raciti GA, Beguinot F and Miele C: Adipose tissue dysfunction as determinant of obesity-associated metabolic complications. Int J Mol Sci 20: 2358, 2019.
25. Amen OM, Sarker SD, Ghildyal R and Arya A: Endoplasmic reticulum stress activates unfolded protein response signaling and mediates inflammation, obesity, and cardiac dysfunction: Therapeutic and molecular approach. Front Pharmacol 10: 977, 2019.
26. Cnop M, Foufelle F and Velloso LA: Endoplasmic reticulum stress, obesity and diabetes. Trends Mol Med 18: 59-68, 2012.
27. Kolb R, Sutterwala FS and Zhang W: Obesity and cancer: Inflammation bridges the two. Curr Opin Pharmacol 29: 77-89, 2016.
28. Fenton JI, Hord NG, Lavigne JA, Perkins SN and Hursting SD: Leptin, insulin-like growth factor-1, and insulin-like growth factor-2 are mitogens in ApcMin/+ but not Apc+/+ colonic epithelial cell lines. Cancer Epidemiol Biomarkers Prev 14: 1646-1652, 2005
29. VanSaun MN: Molecular pathways: Adiponectin and leptin signaling in cancer. Clin Cancer Res 19: 1926-1932, 2013.
30. Hursting SD, Nunez ND, Varticovski L and Vinson C: The obesity-cancer link: Lessons learned from a fatless mouse. Cancer Res 67: 2391-2393, 2007.
31. Cohen DH and LeRoith D: Obesity, type 2 diabetes, and cancer: The insulin and IGF connection. Endocr Relat Cancer 19: F27-F45, 2012.
32. Amin MN, Hussain MS, Sarwar MS, Moghal MM, Das A, Hossain MZ, Chowdhury JA, Millat MS and Islam MS: How the association between obesity and inflammation may lead to insulin resistance and cancer. Diabetes Metab Syndr 13: 1213-1224, 2019.
33. Dobbins M, Decorby K and Choi BCK: The association between obesity and cancer risk: A meta-analysis of observational studies from 1985 to 2011. ISRN Prev Med 2013: 1-16, 2013.
34. Jiralerspong S and Goodwin PJ: Obesity and breast cancer prognosis: Evidence, challenges, and opportunities. J Clin Oncol 34: 4203-4216, 2016.
35. Osman MA and Hennessy BT: Obesity correlation with metastases development and response to first-line metastatic chemotherapy in breast cancer. Clin Med Insights Oncol 9: 105-112, 2015.
36. Rumgay H, Arnold M, Ferlay J, Lesi O, Cabasag CJ, Vignat J, Laversanne M, McGlynn KA and Soerjomataram I: Global burden of primary liver cancer in 2020 and predictions to 2040. J Hepatol 77: 1598-1606, 2022.
37. El-Serag HB and Mason AC: Risk factors for the rising rates of primary liver cancer in the United States. Arch Intern Med 160: 3227-3230, 2000.
38. Ohishi W, Fujiwara S, Cologne JB, Suzuki G, Akahoshi M, Nishi N, Tsuge M and Chayama K: Impact of radiation and hepatitis virus infection on risk of hepatocellular carcinoma. Hepatology 53: 1237-1245, 2011.
39. Larsson S and Wolk A: Overweight, obesity and risk of liver cancer: A meta-analysis of cohort studies. Br J Cancer 97: 1005-1008, 2007
40. Chen Y, Wang X, Wang J, Yan Z and Luo J: Excess body weight and the risk of primary liver cancer: An updated meta-analysis of prospective studies. Eur J Cancer 48: 2137-2145, 2012.
41. Karczewski J, Begier-Krasińska B, Staszewski R, Popławska E, Gulczynska-Elhadi K and Dobrowolska A: Obesity and the risk of gastrointestinal cancers. Dig Dis Sci 64: 2740-2749, 2019.
42. El-Serag HB, Ergun GA, Pandolfino J, Fitzgerald S, Tran T and Kramer JR: Obesity increases oesophageal acid exposure. Gut 56: 749-755, 2007.
43. Long E and Beales IL: The role of obesity in oesophageal cancer development. Ther Adv Gastroenterol 7: 247-268, 2014.
44. Donohoe CL, O'Farrell NJ, Doyle SL and Reynolds JV: The role of obesity in gastrointestinal cancer: Evidence and opinion. Ther Adv Gastroenterol 7: 38-50, 2014.
45. Pati S, Irfan W, Jameel A, Ahmed S and Shahid RK: Obesity and cancer: A current overview of epidemiology, pathogenesis, outcomes, and management. Cancers (Basel) 15: 485, 2023.
46. Rawla P, Sunkara T and Barsouk A: Epidemiology of colorectal cancer: Incidence, mortality, survival, and risk factors. Prz Gastroenterology 14: 89-103, 2019

47. Soltani G, Poursheikhani A, Yassi M, Hayatbakhsh A, Kerachian M and Kerachian MA: Obesity, diabetes and the risk of colorectal adenoma and cancer. BMC Endocr Disord 19: 113, 2019.
48. Hou K, Wu ZX, Chen XY, Wang JQ, Zhang D, Xiao C, Zhu D, Koya JB, Wei L, Li J and Chen ZS: Microbiota in health and diseases. Signal Transduct Target Ther 7: 135, 2022.
49. Barra WF, Sarquis DP, Khayat AS, Khayat BCM, Demachki S, Anaissi AKM, Ishak G, Santos NPC, Dos Santos SEB, Burbano RR, *et al*: Gastric cancer microbiome. Pathobiology 88: 156-169, 2021.
50. Chattopadhyay I, Verma M and Panda M: Role of oral microbiome signatures in diagnosis and prognosis of oral cancer. Technol Cancer Res Treat 18: 1533033819867354, 2019.
51. Yang Y, Dai D, Jin W, Huang Y, Zhang Y, Chen Y, Wang W, Lin W, Chen X, Zhang J, *et al*: Microbiota and metabolites alterations in proximal and distal gastric cancer patients. J Transl Med 20: 439, 2022.
52. Irfan M, Delgado RZR and Frias-Lopez J: The oral microbiome and cancer. Front. Immunol 11: 591088, 2020.
53. Zhao Y, Liu Y, Li S, Peng Z, Liu X, Chen J and Zheng X: Role of lung and gut microbiota on lung cancer pathogenesis. J Cancer Res Clin Oncol 147: 2177-2186, 2021.
54. Ruo SW, Alkayyali T, Win M, Tara A, Joseph C, Kannan A, Srivastava K, Ochuba O, Sandhu JK, Went TR, *et al*: Role of gut microbiota dysbiosis in breast cancer and novel approaches in prevention, diagnosis, and treatment. Cureus 26: e17472, 2021.
55. Nicolaro M, Portal DE, Shinder B, Patel HV and Singer EA: The human microbiome and genitourinary malignancies. Ann Transl Med 8: 1245, 2020.
56. Allen J and Sears CL: Impact of the gut microbiome on the genome and epigenome of colon epithelial cells: Contributions to colorectal cancer development. Genome Med 25: 11, 2019.
57. Collina F, Chiara AD, Renzo AD, Rosa GD, Botti G and Franco R: Chlamydia psittaci in ocular adnexa MALT lymphoma: A possible role in lymphomagenesis and a different geographical distribution. Infect Agent Cancer 7: 8, 2012.
58. Tang T, Wu H, Chen X, Chen L, Liu L, Li Z, Bai Q, Chen Y and Chen L: The hypothetical inclusion membrane protein CPSIT_0846 regulates mitochondrial-mediated host cell apoptosis via the ERK/JNK signaling pathway. Front Cell Infect Microbiol 11: 607422, 2021
59. Olsen I and Yilmaz Ö: Possible role of Porphyromonas gingivalis in orodigestive cancers. J Oral Microbiol 11: 1563410, 2019.
60. Cao S, Li J, Lu J, Zhong R and Zhong H: Mycobacterium tuberculosis antigens repress Th1 immune response suppression and promotes lung cancer metastasis through PD-1/PDl-1 signaling pathway. Cell Death Dis 10: 44, 2019.
61. Littman AJ, Jackson LA and Vaughan TL: Chlamydia pneumoniae and lung cancer: Epidemiologic evidence. Cancer Epidemiol Biomarkers Prev 14: 773-778, 2005.
62. Di Domenico EG, Cavallo I, Pontone M, Toma L and Ensoli F: Biofilm producing Salmonella Typhi: Chronic colonization and development of gallbladder cancer. Int J Mol Sci 18: 1887, 2017.
63. Oehmcke-Hecht S, Mandl V, Naatz LT, Dühring L, Köhler J, Kreikemeyer B and Maletzki C: Streptococcus gallolyticus abrogates anti-carcinogenic properties of tannic acid on low-passage colorectal carcinomas. Sci Rep 10: 4714, 2020.
64. Abdulamir AS, Hafidh RR and Bakar FA: The association of Streptococcus bovis/gallolyticus with colorectal tumors: The nature and the underlying mechanisms of its etiological role. J Exp Clin Cancer Res 30: 11, 2011.
65. Zhou X, Kandalai S, Hossain F and Zheng Q: Tumor microbiome metabolism: A game changer in cancer development and therapy. Front Oncol 12: 933407, 2022.
66. Johansson P, Eckstein A and Küppers R: Biology of ocular adnexal marginal zone lymphomas. Cancers (Basel) 14: 1264, 2022.
67. Yoo JY, Groer M, Dutra SVO, Sarkar A and McSkimming DI: Gut microbiota and immune system interactions. Microorganisms 8: 1587, 2020.
68. Ge Y, Wang X, Guo Y, Yan J, Abuduwaili A, Aximujiang K, Yan J and Wu M: Gut microbiota influence tumor development and Alter interactions with the human immune system. J Exp Clin Cancer Res 40: 42, 2021.
69. Kovács T, Mikó E, Ujlaki G, Sári Z and Bai P: The microbiome as a component of the tumor microenvironment. Tumor Microenviron 2020: 137-153, 2020.
70. Chen Y, Wu FH, Wu PQ, Xing HY and Ma T: The role of the tumor microbiome in tumor development and its treatment. Front Immunol 13: 935846, 2023.
71. He T, Cheng X and Xing C: The gut microbial diversity of colon cancer patients and the clinical significance. Bioengineered 12: 7046-7060, 2021.
72. Zheng D, Liwinski T and Elinav E: Interaction between microbiota and immunity in health and disease. Cell Res 30: 492-506, 2020.
73. Chénard T, Prévost K, Dubé J and Massé E: Immune system modulations by products of the gut microbiota. Vaccines (Basel) 8: 461, 2020.
74. Rawla P and Barsouk A: Epidemiology of gastric cancer: Global trends, risk factors and prevention. Gastroenterol Rev Gastroenterol 14: 26-38, 2018.
75. Hanus M, Parada-Venegas D, Landskron G, Wielandt AM, Hurtado C, Alvarez K, Hermoso MA, López-Köstner F and la Fuente MD: Immune system, microbiota, and microbial metabolites: The unresolved triad in colorectal cancer microenvironment. Front Immunol 12: 612826, 2021.
76. Ilic M and Ilic I: Epidemiology of stomach cancer. World J Gastroenterol 28: 1187-1203, 2022.
77. Lin XJ, Wang CP, Liu XD, Yan KK, Li S, Bao HH, Zhao LY and Liu X: Body mass index and risk of gastric cancer: A meta-analysis. Jpn J Clin Oncol 44: 783-791, 2014.
78. Lee HW, Huang D, Shin WK, de la Torre K, Yang JJ, Song M, Shin A, Lee JK and Kang D: Obesity at early adulthood increases risk of gastric cancer from the health Examinees-Gem (HEXA-G) study. PLoS One 17: e0260826, 2022.
79. Cani PD and Jordan BF: Gut microbiota-mediated inflammation in obesity: A link with gastrointestinal cancer. Nat Rev Gastroenterol Hepatol 15: 671-682, 2018.
80. Doorakkers E, Lagergren J, Engstrand L and Brusselaers N: Eradication of helicobacter pylori and gastric cancer: A systematic review and meta-analysis of cohort studies. J Natl Cancer Inst 108: djw132, 2016.
81. Toh JWT and Wilson RB: Pathways of gastric carcinogenesis, helicobacter pylori virulence and interactions with antioxidant systems, vitamin C and phytochemicals. Int J Mol Sci 21: 6451, 2020.
82. Colotta F, Allavena A, Sica C, Garlanda C and Mantovani A: Cancer-related inflammation, the seventh hallmark of cancer: Links to genetic instability. Carcinogenesis 30: 1073-1081, 2009.
83. Khatoon J, Rai RP and Prasad KN: Role of helicobacter pylori in gastric cancer: Updates. World J Gastrointest Oncol 8: 147-158, 2016.
84. Moyat M and Velin D: Immune responses to Helicobacter pylori infection. World J Gastroenterol 20: 5583-5593, 2014.
85. Udhayakumar G, Jayanthi V, Devaraj N and Devaraj H: Interaction of MUC1 with β-catenin modulates the Wnt target Gene cyclinD1 in H. pylori-induced gastric cancer. Mol Carcinog 46: 807-817, 2007.
86. Hotchin NA, Cover TL and Akhtar N: Cell vacuolation induced by the VacA cytotoxin ofhelicobacter pylori is regulated by the Rac1 GTPase. J Biol Chem 275: 14009-14012, 2000.
87. Yahiro K, Akazawa Y, Nakano M, Suzuki H, Hisatune J, Isomoto H, Sap J, Noda M, Moss J and Hirayama T: Helicobacter pylori VacA induces apoptosis by accumulation of connexin 43 in autophagic vesicles via a Rac1/ERK-dependent pathway. Cell Death Discov 1: 15035, 2015.
88. Caputo R, Tuccillo C, Manzo BA, Zarrilli R, Tortora G, Blanco CD, Ricci V, Ciardiello F and Romano M: Helicobacter pylori VacA toxin up-regulates vascular endothelial growth factor expression in MKN 28 gastric cells through an epidermal growth factor receptor-, cyclooxygenase-2-dependent mechanism1. Clin Cancer Res 9: 2015-2021, 2003.
89. Song X, Xin N, Wang W and Zhao C: Wnt/β-catenin, an oncogenic pathway targeted by H. pylori in gastric carcinogenesis. Oncotarget 6: 35579-35588, 2015.
90. Muhammad JS, Eladl MA and Khoder G: Helicobacter pylori-induced DNA methylation as an epigenetic modulator of gastric cancer: Recent outcomes and future direction. Pathogens 8: 23, 2019.
91. Peterson AJ, Menheniott TR, O'Connor L, Walduck AK, Fox JG, Kawakami K, Minamoto T, Ong EK, Wang TC, Judd LM and Giraud AS: Helicobacter pylori infection promotes methylation and silencing of trefoil factor 2, leading to gastric tumor development in mice and humans. Gastroenterology 139: 2005-2017, 2010.
92. Sato F and Meltzer SJ: CpG island hypermethylation in progression of esophageal and gastric cancer. Cancer 106: 483-493, 2006.
93. Smet A, Kupcinskas J, Link A, Hold GL and Bornschein J: The role of microbiota in gastrointestinal cancer and cancer treatment: Chance or curse?. Cell Mol Gastroenterol Hepatol 13: 857-874, 2022.

94. Engstrand L and Lindberg M: Helicobacter pylori and the gastric microbiota. Best Pract Res Clin Gastroenterol 27: 39-45, 2013.
95. Aviles-Jimenez F, Vazquez-Jimenez F, Medrano-Guzman R, Mantilla A and Torres J: Stomach microbiota composition varies between patients with non-atrophic gastritis and patients with intestinal type of gastric cancer. Sci Rep 4: 4202, 2014.
96. Dias-Jácome E, Libânio D, Borges-Canha M, Galaghar A and Pimentel-Nunes P: Gastric microbiota and carcinogenesis: The role of non-Helicobacter pylori bacteria-A systematic review. Rev Esp Enferm Dig 108: 530-540, 2016.
97. De Witte C, Schulz C, Smet A, Malfertheiner P and Haesebrouck F: Other Helicobacters and gastric microbiota. Helicobacter 21: 62-68, 2016.
98. Tong Y, Gao H, Qi Q, Liu X, Li J, Gao J, Li P, Wang Y, Du L and Wang C: High fat diet, gut microbiome and gastrointestinal cancer. Theranostics 11: 5889-5910, 2021.
99. Arita S and Inagaki-Ohara K: High-fat-diet-induced modulations of leptin signaling and gastric microbiota drive precancerous lesions in the stomach. Nutrition 67-68: 110556, 2019.
100. Colegio OR, Chu NQ, Szabo AL, Chu T, Rhebergen AM, Jairam V, Cyrus N, Brokowski CE, Eisenbarth SC, Phillips GM, *et al*: Functional polarization of tumour-associated macrophages by tumour-derived lactic acid. Nature 513: 559-563, 2014.
101. He C, Cheng D, Peng C, Li Y, Zhu Y and Lu N: High-fat diet induces dysbiosis of gastric microbiota prior to gut microbiota in association with metabolic disorders in mice. Front Microbiol 9: 639, 2018.
102. Kim KA, Gu W, Lee IA, Joh EH and Kim DH: High fat diet-induced gut microbiota exacerbates inflammation and obesity in mice via the TLR4 signaling pathway. PLoS One 7: e47713, 2012.
103. Xiao S, Fei N, Pang X, Shen J, Wang L, Zhang B, Zhang M, Zhang X, Zhang C, Li M, *et al*: A gut microbiota-targeted dietary intervention for amelioration of chronic inflammation underlying metabolic syndrome. FEMS Microbiol Ecol 87: 357-367, 2014.
104. Li N, Xu H, Ou Y, Feng Z, Zhang Q, Zhu Q and Cai Z: LPS-induced CXCR7 expression promotes gastric Cancer proliferation and migration via the TLR4/MD-2 pathway. Diagn Pathol 14: 3, 2019.
105. Zhang XHF, Giuliano M, Trivedi MV, Schiff R and Osborne CK: Metastasis dormancy in estrogen receptor-positive breast cancer. Clin Cancer Res 19: 6389-6397, 2013.
106. Bardou M, Barkun AN and Martel M: Obesity and colorectal cancer. Gut 62: 933-947, 2013.
107. Pischon T and Nimptsch K: Obesity and risk of cancer: An introductory overview in obesity and cancer. Recent Results Cancer Res 208: 1-15, 2016.
108. Torre LA, Siegel RL, Ward EM and Jemal A: Global cancer incidence and mortality rates and trends-an update. Cancer Epidemiol Biomarkers Prev 25: 16-27, 2016.
109. Chaplin A, Rodriguez RM, Segura-Sampedro JJ, Ochogavía-Seguí A, Romaguera D and Barceló-Coblijn G: Insights behind the relationship between colorectal cancer and obesity: Is visceral adipose tissue the missing link? Int J Mol Sci 23: 13128, 2022.
110. Ma Y, Yang Y, Wang F, Zhang P, Shi C, Zou Y and Qin H: Obesity and risk of colorectal cancer: A systematic review of prospective studies. PLoS One 8: e53916, 2013.
111. Matsuo K, Mizoue T, Tanaka K, Tsuji I, Sugawara Y, Sasazuki S, Nagata C, Tamakoshi A, Wakai K, Inoue M, *et al*: Association between body mass index and the colorectal cancer risk in Japan: Pooled analysis of population-based cohort studies in Japan. Ann Oncol 23: 479-490, 2012.
112. Socol CT, Chira A, Martinez-Sanchez MA, Nuñez-Sanchez MA, Maerescu CM, Mierlita D, Rusu AV, Ruiz-Alcaraz AJ, Trif M and Ramos-Molina B: Leptin signaling in obesity and colorectal cancer. Int J Mol Sci 23: 4713, 2022.
113. Milosevic VS, Vukmirovic FC, Krstic MC, Zindovic MM, Stojanovic DL and Jancic SA: Involvement of leptin receptors expression in proliferation and neoangiogenesis in colorectal carcinoma. J BUON 20: 100-108, 2015.
114. Niku M, Pajari AM, Sarantaus L, Päivärinta E, Storvik M, Heiman-Lindh A, Suokas S, Nyström M and Mutanen M: Western diet enhances intestinal tumorigenesis in Min/+ mice, associating with mucosal metabolic and inflammatory stress and loss of Apc heterozygosity. J Nutr Biochem 39: 126-133, 2017.
115. Park S, Koh E, Koo JS, Kim SI, Park BW and Kim KS: Lack of both androgen receptor and forkhead box A1 (FOXA1) expression is a poor prognostic factor in estrogen receptor-positive breast cancers. Oncotarget 8: 82940-82955, 2017.
116. Gheorghe AS, Negru ŞM, Preda M, Mihăilă RI, Komporaly IA, Dumitrescu EA, Lungulescu CV, Kajanto LA, Georgescu B, Radu EA and Stănculeanu DL: Biochemical and metabolical pathways associated with microbiota-derived butyrate in colorectal cancer and omega-3 fatty acids implications: A narrative review. Nutrients 14: 1152, 2022.
117. Mori G, Rampelli S, Orena BS, Rengucci C, De Maio G, Barbieri G, Passardi A, Gardini AC, Frassineti GL, Gaiarsa S, *et al*: Shifts of faecal microbiota during sporadic colorectal carcinogenesis. Sci Rep 8: 10329, 2018.
118. Hannigan GD, Duhaime MB, Ruffin MT IV, Koumpouras CC and Schloss PD: Diagnostic potential and interactive dynamics of the colorectal cancer virome. mBio 9: e02248-e02218, 2018.
119. Fang Y, Yan C, Zhao Q, Xu J, Liu Z, Gao J, Zhu H, Dai Z, Wang D and Tang D: The roles of microbial products in the development of colorectal cancer: A review. Bioengineered 12: 720-735, 2021.
120. Sánchez-Alcoholado L, Ramos-Molina B, Otero A, Laborda-Illanes A, Ordóñez R, Medina JA, Gómez-Millán J and Queipo-Ortuño MI: The role of the gut microbiome in colorectal cancer development and therapy response. Cancers (Basel) 12: 1406, 2020.
121. Schulz MD, Atay C, Heringer J, Romrig FK, Schwitalla S, Aydin B, Ziegler PK, Varga J, Reindl W, Pommerenke C, *et al*: High-fat-diet-mediated dysbiosis promotes intestinal carcinogenesis independently of obesity. Nature 514: 508-512, 2014.
122. Gaines S, van Praagh JB, Williamson AJ, Jacobson RA, Hyoju S, Zaborin A, Mao J, Koo HY, Alpert L, Bissonnette M, *et al*: Western diet promotes intestinal colonization by collagenolytic microbes and promotes tumor formation after colorectal surgery. Gastroenterology 158: 958-970.e2, 2020.
123. Zeng H, Umar S, Rust B, Lazarova D and Bordonaro M: Secondary bile acids and short chain fatty acids in the colon: A focus on colonic microbiome, cell proliferation, inflammation, and cancer. Int J Mol Sci 20: 1214, 2019.
124. Schramm C: Bile acids, the microbiome, immunity, and liver tumors. N Engl J Med 379: 888-890, 2018.
125. Koh GY, Kane A, Lee K, Xu Q, Wu X, Roper J, Mason JB and Crott JW: Parabacteroides distasonis attenuates toll-like receptor 4 signaling and Akt activation and blocks colon tumor formation in high-fat diet-fed azoxymethane-treated mice. Int J Cancer 143: 1797-1805, 2018.
126. Gupta H, Youn GS, Shin MJ and Suk KT: Role of gut microbiota in hepatocarcinogenesis. Microorganisms 7: 121, 2019.
127. Trivedi Y, Bolgarina Z, Desai HN, Senaratne M, Swami SS, Aye SL and Mohammed L: The role of gut microbiome in hepatocellular carcinoma: A systematic review. Cureus 15: e43862, 2023.
128. Plaza-Díaz J, Solís-Urra P, Rodríguez-Rodríguez F, Olivares-Arancibia J, Navarro-Oliveros M, Abadía-Molina F and Álvarez-Mercado AI: The gut barrier, intestinal microbiota, and liver disease: Molecular mechanisms and strategies to manage. Int J Mol Sci 21: 8351, 2020.
129. Schwabe RF and Greten TF: Gut microbiome in HCC-Mechanisms, diagnosis and therapy. J Hepatol 72: 230-238, 2020.
130. Chu H, Williams B and Schnabl B: Gut microbiota, fatty liver disease, and hepatocellular carcinoma. Liver Res 2: 43-51, 2018.
131. Yoshimoto S, Loo TM, Atarashi K, Kanda H, Sato S, Oyadomari S, Iwakura Y, Oshima K, Morita H, Hattori M, *et al*: Obesity-induced gut microbial metabolite promotes liver cancer through senescence secretome. Nature 499: 97-101, 2013.
132. Roh YS and Seki E: Toll-like receptors in alcoholic liver disease, non-alcoholic steatohepatitis and carcinogenesis. J Gastroenterol Hepatol 28: 38-42, 2013.
133. Bartolini I, Risaliti M, Tucci R, Muiesan P, Ringressi MN, Taddei A and Amedei A: Gut microbiota and immune system in liver cancer: Promising therapeutic implication from development to treatment. World J Gastrointest Oncol 13: 1616-1631, 2021.
134. Allsopp P, Possemiers S, Campbell D, Gill C and Rowland I: A comparison of the anti-cancer properties of isoxanthohumol and 8-prenylnaringenin using in vitro models of colon cancer. Biofactors 39: 441-447, 2013.
135. Higashimura Y, Naito Y, Takagi T, Uchiyama K, Mizushima K, Ushiroda C, Ohnogi H, Kudo Y, Yasui M, Inui S, *et al*: Protective effect of agaro-oligosaccharides on gut dysbiosis and colon tumorigenesis in high-fat diet-fed mice. Am J Physiol Gastrointest Liver Physiol 310: G367-G375, 2016.

136. Costabile A, Fava F, Röytiö H, Forssten SD, Olli K, Klievink J, Rowland IR, Ouwehand AC, Rastall RA, Gibson GR and Walton GE: Impact of polydextrose on the faecal microbiota: A double-blind, crossover, placebo-controlled feeding study in healthy human subjects. Br J Nutr 108: 471-481, 2012.
137. Shields CE, Van Meerbeke SW, Housseau F, Wang H, Huso DL, Casero RA Jr, O'Hagan HM and Sears CL: Reduction of murine colon tumorigenesis driven by enterotoxigenic bacteroides fragilis using cefoxitin treatment. J Infect Dis 214: 122-129, 2016.
138. Hou H, Chen D, Zhang K, Zhang W, Liu T, Wang S, Dai X, Wang B, Zhong W and Cao H: Gut microbiota-derived short-chain fatty acids and colorectal cancer: Ready for clinical translation?. Cancer Lett 526: 225-235, 2022.
139. Son MY and Cho HS: Anticancer effects of gut microbiota-derived short-chain fatty acids in cancers. J Microbiol Biotechnol 33: 849-856, 2023.
140. Schneider KM, Mohs A, Gui W, Galvez EJC, Candels LS, Hoenicke L, Muthukumarasamy U, Holland CH, Elfers C, Kilic K, *et al*: Imbalanced gut microbiota fuels hepatocellular carcinoma development by shaping the hepatic inflammatory microenvironment. Nat Commun 13: 3964, 2022.
141. Yu LX and Schwabe RF: The gut microbiome and liver cancer: Mechanisms and clinical translation. Nat Rev Gastroenterol Hepatol 14: 527-539, 2017.
142. Patel AH, Li Y, Minacapelli CD, Catalano K and Rustgi V: Reduction in gastrointestinal cancers in cirrhotic patients receiving rifaximin vs lactulose only therapy for hepatic encephalopathy. Cureus 15: e35259, 2023.
143. Ting NLN, Lau HCH and Yu J: Cancer pharmacomicrobiomics: Targeting microbiota to optimise cancer therapy outcomes. Gut 71: 1412-1425, 2022
144. de Clercq NC, van den Ende T, Prodan A, Hemke R, Davids M, Pedersen HK, Nielsen HB, Groen AK, de Vos WM, van Laarhoven HWM and Nieuwdorp M: Fecal microbiota transplantation from overweight or obese donors in cachectic patients with advanced gastroesophageal cancer: A randomized, double-blind, placebo-controlled, phase II study. Clin Cancer Res 27: 3784-3792, 2021
145. Napolitano M and Covasa M: Microbiota transplant in the treatment of obesity and diabetes: Current and future perspectives. Front Microbiol 11: 590370, 2020.
146. Davar D, Dzutsev AK, McCulloch JA, Rodrigues RR, Chauvin JM, Morrison RM, Deblasio RN, Menna C, Ding Q, Pagliano O, *et al*: Fecal microbiota transplant overcomes resistance to anti-PD-1 therapy in melanoma patients. Science 371: 595-602, 2021.
147. Xu H, Cao C, Ren Y, Weng S, Liu L, Guo C, Wang L, Han X, Ren J and Liu Z: Antitumor effects of fecal microbiota transplantation: Implications for microbiome modulation in cancer treatment. Front Immunol 13: 949490, 2022.
148. Zhao LY, Mei JX, Yu G, Lei L, Zhang WH, Liu K, Chen XL, Kołat D, Yang K and Hu JK: Role of the gut microbiota in anticancer therapy: from molecular mechanisms to clinical applications. Signal Transduction Target Ther 8: 201, 2023.