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Review

Microbiota Alterations in Gastrointestinal Cancers

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Featured Application: Microbiome is being intensively studied in the context of many diseases, as well as health maintenance. Proper understanding of microbiota alterations in gastrointestinal cancers on the taxonomic and functional level (i.e., metabolic pathways and metabolites) creates good basics for further therapy and biomarker development.

Abstract: Commensal microbiota plays a critical role in the maintenance of human health. Microbes influence energy metabolism and nutrient absorption and help defend the host organism against pathogens. The composition of the gut microbiota is delicately balanced, and any alterations may lead to proinflammatory immune responses and initiation of disease processes, including cancer. Experimental evidence indicates that the human intestinal microbiota can influence tumour development and progression in the gastrointestinal tract by damaging DNA, activation of oncogenic signaling pathways, production of tumour-promoting metabolites, and suppression of the anti-tumour immune response. The aim of this article was to outline differences in human microbiota between healthy subjects and patients with gastrointestinal malignancies such as esophageal, stomach, liver, biliary tract, pancreas and colon inflammations, and cancers. A better understanding of microbiota changes in various gastrointestinal malignancies will enable a greater insight into the relationship between human microbiota composition and cancer development.

Keywords: cancer; gastrointestinal cancer; microbiota

1. Introduction

The human microbiota is composed of bacteria, archaea, viruses, and eukaryotic microbes that reside in and on our bodies. Commensal microbes are critical for the maintenance of human health and play an integral role in energy metabolism, absorption of nutrients, and defense against pathogens. Commensal microbiota exists within a delicate balance and is strongly influenced by environmental factors, such as obesity, diet, or drug intake. Changes in microbiota composition may contribute to aberrant proinflammatory immune responses, susceptibility to invading pathogens, and initiation of disease processes, including cancer. Changes in gut microbiota could also contribute to the pathogenesis of gastrointestinal cancers [1].

Gastrointestinal cancers such as those of the esophagus, stomach, liver, biliary tract pancreas, and colon account for one-third of total cancer incidence and mortality in developing countries. The growing prevalence of obesity in nearly all regions of the world, as well as alcohol overuse and smoking, are known key agents that increase the incidence of gastrointestinal cancers, as well as gut hormones and nonalcoholic fatty liver disease (NAFLD). Additionally, experimental evidence indicates that the human intestinal microbiota can influence tumour development and progression in

the gastrointestinal tract by damaging DNA, activating oncogenic signaling pathways, initiating the production of tumour-promoting metabolites, and suppressing the antitumor immune response [2,3].

2. Esophageal Cancers

Esophageal cancers (ECs) are the eighth most frequent cancer worldwide. Moreover, EC is characterized by its aggressive progression and a poor five-year survival rate of about 20% [4,5]. The most frequently-characterized forms of EC are squamous cell carcinomas (ESCCs) and adenocarcinomas (EACs) [4]. Even though both ECs share similar key risk factors, for example, smoking, alcohol overuse, unhealthy diet, and obesity [6], the incidence and etiology vary significantly between ESCC and EA.

For a long time, ESCC accounted for about 87% esophageal cancers; however, in the last few years, adenocarcinoma has become the leading cause of esophageal cancer [7,8]. ESCC arises from the flat cells of the esophagus mucosa and its incidence is strongly related with age, socioeconomic status, alcohol and tobacco overuse, obesity, and human papilloma virus (HPV) infection [7]. Mutations connected with ESCC include mainly amplifications of ccnd1 and sox2 and/or tp63 [3,4].

Even though genetic factors influence EAC outcome, that is, amplification of erbb2, vegfa, and gata4 and gata6 [3], this malignancy is the most strongly correlated with the occurrence of gastroesophageal reflux disease (GERD). It has been demonstrated that the odds ratio for esophageal adenocarcinoma was 7.7 (95 percent confidence interval (CI), 5.3 to 11.4) among persons with recurrent symptoms of reflux compared with people without such symptoms and 43.5 (95 percent confidence interval, 18.3 to 103.5) among persons with long-standing and severe symptoms of reflux [9]. GERD leads to persistent inflammation of esophagus tissues. Chronic esophagitis leads to the development of metaplastic lesions, which can result in Barrett's esophagus (BE), that is, metaplastic changes in the esophagus mucosa. [3,6]. BE is strongly connected with EAC outcome; Hvid-Jensen et al. reported that patients with BE exhibited a 30- to 60-fold increase in the incidence of EAC [7].

2.1. Microbiota in Physiological Esophagus

Early studies on healthy esophagus microbiota were conducted by Galiardi in 1998. Galiardi et al. reported the presence of *Gemella*, *Klebsiella*, *Citrobacter*, *Haemophilus*, *Helicobacter*, and *Escherichia* in healthy human esophagus [10]; this was later confirmed by Pei et al. (2005) on healthy human esophagus microbiota (study on 24 patients: 9 with normal esophageal mucosa, 12 with gastroesophageal reflux disease (GERD), and 3 with Barrett's esophagus). Using 16S sequencing, Pei et al. have identified 95 genera in six phyla: Firmicutes (e.g., *Streptococcus*), Bacteroides (e.g., *Prevotella*), Actinobacteria (e.g., *Rothia*), Proteobacteria (e.g., *Haemophilus*), Fusobacteria (e.g., *Fusobacterium*), and TM7 [11]. Norder et al., in 2013, using aerobic and anaerobic culture examination of esophageal samples, found *Streptococcus*, *Neisseria*, *Haemophilus*, and *Prevotella* genera to predominate among bacteria in healthy human esophagus [12]. *S. viridans* is being characterized as the most frequent microorganism inhabiting normal esophagus in humans, with studies on animal and human models indicating that *S. viridans* represents about 95% of the esophagus microbiota [3,12] (aerobic and anaerobic culture examination of 40 oral, upper esophageal, and lower esophageal mucosa samples). However, it must be taken into consideration that a significant part of human gut microbiome is not-cultivable; therefore, results from Galiardi et al. as well as Norder et al. should be interpreted carefully.

2.2. Microbiota in Gastroesophageal Reflux Disease and Barrett's Esophagus

Gastroesophageal reflux disease (GERD) is a common, but dangerous condition of the upper gastrointestinal tract. GERD develops as a result of constant irritation of the esophagus by stomach acids. The disease arises from motor abnormalities or anatomical factors such as obesity or hiatal hernia [13]. Without treatment, GERD might result in the development of Barrett's esophagus (BE). BE affects the distal esophagus, that is, normal stratified squamous are replaced by columnar mucosa with intestinal specialized metaplasia. BE is a premalignant condition that might directly result in esophageal adenocarcinoma [14].

Alterations in the esophageal microbiota are observed in GERD and BE, suggesting that the oral microbiota may play a potential role in disease development. Yang et al., in a 16S rRNA gene survey on a group of 34 patients with normal esophagus, GERD, and BE, have reported that BE and GERD associated microbiota is characterized by a greater ratio of Gram-negative anaerobes/microaerophiles (Bacteroidetes, Proteobacteria, Fusobacteria, and Spirochaetes). The results may suggest that changes in composition of the microbiota in the distal esophagus may lead to inflammation and intestinal metaplasia, as Gram negative bacteria produce lipopolysaccharide (LPS), which activates the innate immune response [15].

Liu et al. [6] found the microbiota of patients with GERD and BE to be colonized mainly by *Veillonella*, *Prevotella*, *Neisseria*, and *Fusobacterium* species; species that are not detected in the microbiota of the normal esophagus. Later studies also found *Campylobacter* spp. and *E. coli* [3] to be present in abnormal human esophagus. Gagliardi et al. highlight differences in microbial composition between patients with normal esophagus, GERD, and BE; *Streptococcus* was the most abundant genus in three study groups (20% of all bacteria detected), but was lower in the BE study group. The GERD-associated esophagitis microbiota was significantly enriched in *Veillonella*, *Haemophilus*, *Pasteurella*, *Neisseria*, and *Fusobacterium*, which were almost undetectable in healthy subjects. The microbiota related to BE was comparable to that of the reflux esophagitis-associated microbiota; however, it displayed a higher prevalence of *Veillonella*, *Achromobacter*, and *Actinobacillus* (not recognized in reflux esophagitis microbiota) [10] (Table 1).

Table 1. Differences in esophagus microbiota between patients with Barrett's esophagus, reflux esophagitis, and healthy subjects (distribution of clones at the phylum level).

Phylum	Normal Esophagus n = 147	Reflux Esophagitis n = 139	Barrett's Esophagus n = 138
Proteobacteria	72	60	28
Firmicutes	59	46	76
Bacteroidetes	12	14	19
Fusobacteria	-	14	12
Actinobacteria	5	3	3
TM7	-	3	-

Despite interesting results and well-performed statistical analysis, Yang et al. as well as Liu et al. did not consider other, non-bacterial factors that might influence esophagus inflammation such as smoking, diet, or medical conditions. It would be necessary to extend the analysis by adding the aforementioned variables in order to verify if the increase in the number of Gram-negative bacteria still significantly impacts GERD and BE development. Moreover, as mentioned before, Galiardi et al.'s study was limited by the culture base techniques that are unable to thoroughly represent the microbime composition.

Bacterial population in the distal esophagus was examined by Liu et al. [6] using biopsy samples from 18 subjects (6 subjects with normal eosphagus, 6 subjects with reflux esophagitis, and 6 subjects with Barrett's esophagus). From the average of 350 clones in each of subjects, 40 were randomly selected and sequenced. Then, 240 clones (40 clones from each subject) yielded 147 16S rDNA sequences, classified into four phyla (normal esophagus); 139 16S rDNA sequences, classified into six phyla (reflux esophagitis); and 138 16S rDNA sequences, classified into five phyla (Barrett's eosphagus). Study indicates that Proteobacteria and Firmicutes presence is dominant in all study groups, however, a significant decrease of Proteobacteria is noticed in Barrett's esophagus patients. Fusobacteria, not present in normal esophagus microbiota, is present in reflux esophagitis and Barrett's esophagus.

2.3. Microbiota in Esophagus Cancer

Microflora is reported to impact the development of gastrointestinal (GI) cancers, including esophagus adenocarcinoma. The microbiota of the upper digestive tract in cases of esophageal malignancies is reported to be dominated by bacterial pathogens [16,17]. Narikiyo et al. found the

oral microflora of patients with esophageal adenocarcinoma to be dominated by *Treponema denticola*, *Streptococcus mitis*, and *Streptococcus anginosus*; oral pathogens strongly associated with periodontitis [18]. Harmful bacteria influence cancer development by the production of pro-cancerogenic compounds such as superoxide and hydrogen sulfide, produced by *Enterococcus faecalis* and *Fusobacterium*, respectively; their release causes a cancer-promoting inflammatory response, which is mainly mediated by innate immunity [17]. *Fusobacterium nucleatum*, a species strongly associated with colorectal cancer development, was reported to be present in about 23% of samples taken from patients with esophageal cancers. Moreover, the presence of *F. nucleatum* frequently relates to poorer prognosis and more aggressive tumour behavior [3]. Gosh et al. reported that the components of the *F. nucleatum* cell wall strongly activate the immune system and lead to robust activation of chemokine (C-C motif) ligand 20 (CCL20), a chemokine linked inter alia with ovarian, colorectal, and pancreatic cancers [19,20] (results obtained via stimulation of human primary oral epithelial cell cultures with *F. nucleatus* cell wall fractions).

Esophagus cancer-related microbiota varies between ESCC and EAC. The results of further analysis on differences in microbiota composition in EAC and ESCC performed by various scientific groups can be found in Table 2 [3,16,18,21,22].

Table 2. Oral microbiota composition differences between esophageal squamous cell carcinoma and esophagus adenocarcinoma (distribution of clones at the genus and species levels).

EAC	ESCC
Actinomyces cardiffensis	*Bergeyella oral taxon 322*
Selenomonas oral taxon 134	*Porphyromonas*
Streptococcus anginosus	*Prevotella*
Streptococcus mitis	*Streptococcus*
Tannerella forsythia	*Bulleidia*
Treponema denticola	*Cardiobacterium*
Veillonella oral taxon 917	*Catonella*
-	*Corynebacterium*
-	*Lautropia*
-	*Moryella*
-	*Peptococcus*
-	*Prevotella oral taxon 306*
-	*Neisseria weaver*
-	*Treponema vincentii*
Corynebacterium durum	-
Haemophilus oral taxon 908	*Aggregatibacter paraphrophilus (commensal)*
Lachnoanaerobaculum umeaense	-
Neisseria flavescens	-
Neisseria sicca	-
Oribacterium parvum	-
Prevotella nanceiensis	-
Solobacterium moorei	-
Streptococcus pneumoniae	-

Abbreviations: ESCC—esophageal squamous cell carcinoma, EAC—esophagus adenocarcinoma.

Various studies [16,18,21,22] present changes in esophagus microbiota in patients with ESCC and EAC. An increase in bacteria related to periodontal disease and decrease in commensal bacteria and butyrate producers was observed among patients.

Mouthwash samples of 81 EAC cases with matched 160 controls, and 25 ESCC cases with 50 matched controls. 16S rRNA gene sequencing [16]; 69 esophageal cancer tissues, PCR amplification of various bacterial 16S ribosomal DNAs and Northern blot and slot blot analyses [18]; saliva samples of 87 incident and histopathologically diagnosed ESCC cases, 63 subjects with dysplasia, and 85

healthy controls amplification of V3–V4 region of 16S rRNA and sequencing by 454-pyrosequencing platform [21]; 325 esophageal cancer biopsy, quantification of *F. nucleatum* DNA [22].

It has been demonstrated that the prevalence of *Actinomyces* is greater in EAC. *Actinomyces* is a common genus residing on the surfaces of the oral mucosa and has also been found in the human pharynx; however, in the case of tissue injury, their presence might lead to endogenous infection known as actinomycosis [23]. Actinomycosis causes the development of chronic inflammation in soft tissues, leading to necrosis and the formation of yellowish sulphur granules [24]. *Tannerella forsythia*, a Gram negative, anaerobic bacterium, strongly induces pro-inflammatory cytokines such as interleukin (IL)-1β and IL-6 by CD4 (cluster of differentation 4) + T helper cells and tumor necrosis factor (TNF-α). Moreover, multiple virulence factors such as trypsin-like proteases and cysteine-like proteases can cause the degradation of protein components within infected tissues, which facilitates tissue colonization by other pathogens [25]. EAC microbiota have also been shown to be enriched with bacteria related to periodontal disease, that is, *Veillonella* [26] *Selenomonas*, and *Treponema denticola* [27]. *T. denticola* has been mostly associated with severe periodontitis; however, it has been suggested that bacterial virulence factors, especially chymotrypsin-like proteinase (Td-CTLP), might contribute to cancer development. Nieminen et al. reported that Td-CTLP exhibit regulatory activity on proteins critical for the regulation of tumour microenvironment and inflammation [27]. Interestingly, an increase in *T. denticola* abundance has also been linked to pancreatic cancer. Both EAC and ESCC were enriched in *Streptococcus* genera, and it has been found that enrichment in *Streptococcus* might lead to cancer development, as these bacteria strongly activate the immune system of the host. Narikiyo et al. reported that *Streptococcus mitis* and *Streptococcus anginosus* increase the expression of IL-8, a strong chemotactic factor for immune cells, and growth-regulated protein α (GROα), a chemokine involved in inflammation and tumorigenesis [18,28].

The microflora of ESCC patients has also been reported to be enriched in bacterial genera linked to periodontitis and inflammation, that is, *Porphyromonas*, *Treponema*, *Streprococcus*, and *Prevotella*. *Prevotella* is a member of commensal human microflora, so its presence seems explicable in the microflora of ESCC cancer patients; however, it is also linked to periodontitis, rheumatoid arthritis, and low-grade systemic inflammation. It might contribute to cancer development by stimulating epithelial cells to produce proinflammatory cytokines, that is, IL-8, IL-6 and CCL20, a chemokine linked directly to cancer development [29]. Considerable interest has been focused on a possible link between the presence of *Porphyromonas* and the development of oral, gastrointestinal, and pancreatic cancers. Geng et al. (model exposing human immortalized oral epithelial cells to *P. gingivalis* at a low multiplicity of infection for 5–23 weeks) and Binder Gallimidi et al. (murine model of periodontitis-associated oral tumorigenesis) note that Porphyromonas *gingivalis* robustly induces inflammatory response and promotes the proliferation of cyclin D1, matrix metalloproteinase-9 (MMP-9), and heparinase [30,31]. Moreover, long-term exposure to *P. gingivalis* stimulates cell migration and invasion abilities [31].

In both types of esophageal cancers, a strong decrease in commensal microflora can be observed, which may be associated with changes occurring in tissues undergoing carcinogenic transformation. It is worth noting that a decrease occurs in *Moryella* and *Lachnoanaerobaculum umeaense*, commensal bacteria that produce butyrate, a short chain fatty acid (SCFA) that has been frequently reported to exhibit anticancer activity [32]. A decrease in *Lautropia* genus has also been observed in heavy smokers, which can suggest that its decrease is not necessarily a direct result of cancer development [33].

Interestingly, it has been found that specific esophagus microbiota composition might not only be associated with higher cancer risk, but can also lower the chance of malignancy development [16]. Infection with *Helicobacter pylori*, a well-studied bacterium connected with gastric cancer, is reported to lower the risk of esophagus cancer development. Case-control studies have proposed that gastritis, caused by *H. pylori* infection, might prevent GERD and BE development. One hypothesis suggests that *H. pylori* infection prevents esophageal disease development by a pathway dependent on the brain–gut axis; however, the subject needs further investigation [3,34].

3. Gastric Cancer

Globally, gastric cancer (GC) is the fourth most common cancer. GC is being described as one of the most aggressive gastrointestinal malignancies, with an average five-year survival rate of about 20% [35,36]. Gastric cancer development is strongly affected by environmental factors and individual lifestyle. A diet rich in salt and salt-preserved foods, meat, and fat, but low in fiber, obesity, alcohol overuse, and heavy smoking strongly increases the risk of GC development. Moreover, GC is more frequent in men than in women, and most cases are diagnosed in older patients [35,36]. In most cases (95%–90%), GCs develops sporadically. According to the Lauren classification, two main histological subtypes of gastric cancers are differentiated: intestinal and hereditary diffuse gastric cancer (HDGC) [36]. The intestinal type of GC is the most common, accounting for approximately 54% of cases, while the HDGC type accounts for 15%–32% of GC incidences [36].

Most HDGCs are inherited in an autosomal dominant way. Their development is most frequently caused by germline mutations in the E-cadherin *cdh1* gene; however, sporadic mutations in *ctnna1*, *map3k6*, *insr*, *fbxo24*, and *dot1l* genes are also being identified [37]. The mean age at diagnosis is 38 years. The incidence of malignancy is comparable in all age groups and genders. HDGCs affect the corpus or the entire stomach and are characterized by rapid progression and poorer prognosis [37].

The intestinal type of gastric cancer develops in a progressive, inflammation-driven manner. Chronic gastritis evolves into atrophic gastritis and intestinal metaplasia, leading to dysplasia and finally adenocarcinoma. The intestinal type of GC mostly affects the antrum and incisura of the organ and is most frequent in men and older subjects. The risk factors for the development of gastric adenocarcinoma are obesity; alcohol overuse; cigarette smoking; a diet rich in salt and fat; diseases such as pernicious anemia; and, most importantly, *H. pylori* infection [35]. We will not discuss hereditary diffuse gastric cancer in this article.

3.1. Microbiota in Physiological Stomach

The human stomach, owing to its acidity, was for a long time considered a germ-free organ. However, the discovery of *H. pylori* and its impact on GC development have revealed mechanisms by which bacteria can overcome low pH and colonize the abdomen. Gastric microbial density is estimated at around 10^2 to 10^4 colony-forming units (CFU)/mL. This number might vary depending on changes in local pH, diet, or drug intake [38,39]. Data obtained from healthy patients indicate that the dominant phyla of the gastric microbiota are Proteobacteria, Firmicutes, Actinobacteria, Bacteroidetes, and Fusobacteria [40] (23 gastric endoscopic biopsy samples, 16S rDNA clone library approach). The most abundant genera are *Lactobacillus*, *Propionibacterium* [40]. *Enterococcus*, *Streptococcus*, *Staphylococcus*, *Pseudomonas*, and *Stomatococcus* [41] (8 biopsy specimens from patients with *Helicobacter pylori*-associated gastritis and 5 controls, temporal temperature gradient gel electrophoresis (TTGE) of PCR-amplified 16S rDNA fragments), *Clostridium*, and *Veillonella* [42] (24 samples obtained with special catheter, selective culture media for aerobic and anaerobic microorganisms and yeasts). Until today, research aiming to determine composition of healthy stomach related microbiota was conducted on very small study groups, which does not allow to infer about the entire population. It is understandable as gastric endoscopy and biopsy collection is an invasive examination, but bigger study groups are required to establish core gastric microbiota.

3.2. Microbiota in Gastritis

It is worth describing changes in gastric microflora during gastritis as chronic inflammation of gastric tissues frequently leads to the development of gastric cancer [43]. Patients with gastritis or gastric cancer often display different gastric microbiota to healthy subjects. A study of 81 individuals with chronic gastritis and 54 patients with gastric carcinoma found the gastric microflora of gastritis patients to be more abundant and diverse than that of the cancer. It was also found that the microbial community of patients with chronic gastritis was dominated by *Helicobacter*, *Neisseria*, *Prevotella*, and

Streptococcus genera [44]. *H. pylori* infection is a very well-studied risk factor for GC development; however, few studies describe the possible role of other bacteria in GC development. One of these found the five most abundant genera gastric mucosal biopsies from patients with gastritis to be *Streptococcus*, *Prevotella*, *Neisseria*, *Haemophilus*, and *Porphyromonas*, which together accounted for 70.5% of all microbial clones [45].

Gao et al., in a culture-independent microbiome analysis, compared gut microbiota composition in three groups of individuals with gastritis: patients with current *H. pylori* infection, patients that have undergone *H. pylori* infection in the past, and those without *H. pylori*. The results indicated that the most abundant phyla in all three study groups were Bacteroidetes, Firmicutes, and Proteobacteria, with mean relative abundances of 54.77%, 31.37%, and 12.91%, respectively, accounting for 99.05% of faecal microbiota. Patients with current *H. pylori* infection exhibited a decrease in the abundance of *Acidovorax* and *Rhodococcus* and an increase in *Gemella* and *Erysipelotrichaceae UCG 004* [46]. This is an interesting finding, as *Rhodococcus* is an opportunistic pathogen and *Acidovorax* has been linked to colorectal neoplasia owing to its ability to increase the metabolism of nitro-aromatic compounds and trigger the immune response [47], while *Gamella* and *Erysipelotrichaceae* are members of commensal oral and gut microflora, respectively [5,48].

3.3. Microbiota in Gastric Adenocarcinoma

Ferreira et al. reported that samples of gastric microflora obtained from gastritis patients tended to be more abundant than those obtained from gastric cancer patients. In addition, the gastric microbiota of GC patients was dominated by intestinal commensals. Study reported that both study groups were dominated by five phyla: Proteobacteria (69.3%), Firmicutes (14.7%), Bacteroidetes (9.0%), Actinobacteria (4.3%), and Fusobacteria (1.3%). GC-related gastric microflora was characterized by decrease in the genera *Helicobacter*, *Fusobacterium*, and *Neisseria*, as well as some members of the Bacteroidetes. The gastric microflora of the GC patients was reported to be enriched in Proteobacteria such as the *Xanthomonadaceae* and *Enterobacteriaceae*, as well as genera such as *Citrobacter*, *Phyllobacterium*, and *Achromobacter*. In addition, the gastric microbiota of GC patients was enriched in intestinal mucosa commensals, that is, *Lactobacillus*, *Phyllobacterium*, *Clostridium*, and *Rhodococcus* [44]. Similar results were obtained by Lertpiriyapong et al., suggesting that the presence of intestinal microbiota in stomach might be linked to GC development [49,50]. This research must be also considered carefully, as it was performed on a murine model with artificially induced microflora. It is known that microbiota-related analyses are able to give only a short overview owing to differences in mouse and human gastric tract structure and metabolism, among others. The gastric microbiota of GC patients was shown to be enriched in nitrosating bacteria; such nitrate-reducing activity increases the intragastric concentrations of nitrite and *N*-nitroso compounds, which have been reported to increase the risk of GC development [51,52].

Even though *H. pylori* is the main pathogen increasing the risk of GC, studies reported that gastric colonization by non-*Helicobacter pylori* bacteria, such as Actinobacteria, Bacteroides, Firmicutes, Fusobacteria, and Proteobacteria, might be related to higher risk of GC development. However, the mechanism by which this microbe can influence the outcome of GC is not clearly understood [44,49,53]. Some Bacteroides and Fusobacteria members have been found to exhibit cancer promoting activity. It has been reported that infection with *Bacteroides fragilis* is directly linked to colorectal cancer development. *B. fragilis* toxin (BFT) strongly stimulates the immune system and influences epithelial homeostasis through E-cadherin cleavage, leading to extensive cell proliferation [54]. In addition, *B. fragilis* lipid A has been found to be structurally similar to *H. pylori* lipid A [55]. It is thus possible that, while translocating from the intestine to the stomach during the development of GC, *B. fragilis* produces BFT and promotes GC development. *Fusobacterium nucleatum* has been frequently isolated from stool samples of colorectal cancer (CRC) patients. It has been suggested that the bacterium influences CRC development owing to its ability to induce an inflammatory response (especially stimulation of TNF-α and N Fκ-B (nuclear factor kappa B) production) and bind E-cadherin to the

epithelial cell [56]. It has also been reported that increased abundance of Proteobacteria is a sign of overall dysbiosis in gut microbiota and has been linked to colitis and colorectal cancer outcome. Studies reveal that impairments in the innate immune system promote the outgrowth of Proteobacteria, and that increases in the Proteobacteria number enhance the immune response in the host gut, leading to colitis development [57,58]. Table 3 illustrates bacterial signatures of healthy stomach microbiome, as well as gastritis and cancer-related microbiota.

Table 3. Bacterial signatures of healthy stomach microbiome as well as gastritis and cancer related stomach microbiota.

State	Bacterial Signatures
Healthy stomach	Proteobacteria, Firmicutes, Actinobacteria, Bacteroidetes, and Fusobacteria [40] *Lactobacillus*, *Propionibacterium* [40] *Enterococcus*, *Streptococcus*, *Staphylococcus*, *Pseudomonas*, *Stomatococcus* [41] *Clostridium*, *Veillonella* [42]
Gastritis	*Helicobacter*, *Neisseria*, *Prevotella*, and *Streptococcus genera* [44] *Streptococcus*, *Prevotella*, *Neisseria*, *Haemophilus*, *Porphyromonas* [45]
Gastric cancer	Proteobacteria (*Xanthomonadaceae* and *Enterobacteriaceae*, as well as genera such as *Citrobacter*, *Phyllobacterium*, and *Achromobacte*), Firmicutes (*Lactobacillus*, *Clostridium*), Bacteroidetes, Actinobacteria (*Rhodococcus*), and Fusobacteria [44,49,50] oral bacteria (*Peptostreptococcus*, *Streptococcus*, and *Fusobacterium*) [52] bacteria harbouring nitrosating enzymes [51,52]

3.4. Gastric Cancer and H. pylori

Even though *Helicobacter pylori* infection and its consequences are being extensively studied, its presence is associated with a growing number of diseases. *H. pylori* has been linked to multiple sclerosis; celiac disease; asthma; anaemia; insulin resistance; diabetes; and, most importantly, gastric cancer [59].

Although the cycle leading from *H. pylori* infection to GC development has been well described, little is known about the impact of *H. pylori* on the composition of the gastric microbiota. Chronic *H. pylori* infection damages the gastric parietal cells responsible for acid secretion. Higher stomach pH creates a favourable environment for intestinal flora (IF) to develop. Following Hp infection, the microbiota of GC patients was reported to demonstrate higher numbers of *Streptococcus*, *Lactobacillus*, *Veillonella*, and *Prevotella* than subjects without *H. pylori* infection (murine model with artificially induced microflora). It has been suggested that IF accelerates Hp-associated GC, however, little is known about the possible mechanism [50]. A study on murine model reported that mice with both Altered Schaedler's flora and *H. pylori* infection exhibited a more severe GC outcome than germ-free mice or mice infected only with *H. pylori*; in addition, a decrease in *Clostridum* and *Bacteroides* species with significant a increase in *Lactobacillus murinus* was reported, suggesting that the presence of IF might enhance the immune response, and thus accelerate the outcome of GC [50]. Similar results were obtained by Lofgren et al., who reported that GIN (gastrointestinal intraepithelial neoplasia) develops significantly more slowly in germ-free mice or mice with *H. pylori* consociation compared with specific pathogen-free *H. pylori* infected animals. Additionally, Lofgren et al. reported an increase in *Firmicutes* with a simultaneous decrease in *Bacteroidetes* and *Cyanobacteria* in the stomach of the mice (microbiota composition quantified by pyrosequencing) [60].

Interestingly, Ferreira et al. reported that the level of *H. pylori* decreases significantly in GC-related microbiota and the microbial community was enriched in non-Helicobacter *Proteobacteria* ($r = -0.59$, $p < 0.0001$), *Firmicutes* ($r = -0.49$, $p < 0.0001$), *Bacteroidetes* ($r = -0.43$, $p < 0.0001$), and *Actinobacteria* ($r = -0.54$, $p < 0.0001$). A study also reported a decrease in *H. pylori* abundance in GC patients, that the presence of *H. pylori* was associated with co-colonization by Bacteroidetes and Fusobacteria, and that the GC microbiota was dominated by Proteobacteria [44].

4. Pancreatic Cancer

Pancreatic cancer is known as one of the deadliest cancers worldwide. According to the American Cancer Society, in 2019, about 56,770 new cases of pancreatic cancer will be diagnosed and about 45,750 patients will die of this malignancy in the USA alone [www.cancer.org]. The overall five-year survival rate is about 6% [61]. The malignancy is highly fatal owing to a lack of effective screening methods and the fact that current treatment modalities fail to treat the disease [61–63]. The incidence of pancreatic cancer is similar in developing and developed countries and both sexes [www.cancer.org].

The pancreas is composed of exocrine and endocrine cells. Exocrine cells form the exocrine glands and the ducts by which digestive enzymes and bicarbonate ions reach the small intestine, while the endocrine cells constitute the islets of Langerhans, which produce hormones such as insulin or glucagon [64]. Pancreatic cancers are distinguished according to the cells from which they originate, that is, exocrine cancers (adenocarcinomas) and pancreatic endocrine tumors (also named pancreatic neuroendocrine tumors, or NETs) [61].

Exocrine pancreatic cancers originate from exocrine pancreatic cells and are the most common pancreatic cancers. Most exocrine pancreatic cancers are adenocarcinomas (pancreatic ductal adenocarcinoma, or PDAC) and account for about 85% of all pancreatic cancer cases [61]. PDAC has been described as a cancer associated with chronic inflammation, with pancreatitis being one of the main causes of its development. Patients with hereditary autoimmune pancreatitis have an estimated 40% risk of PDAC development, whereas those with chronic pancreatitis have a 13-fold greater risk [62].

Risk factors for PDAC development are smoking, obesity, a diet rich in highly processed food and meat, diabetes (both type I and type II), allergies, male sex, and age—over 80% of pancreatic cancers develop between the ages of 60 and 80 years [65,66]. It is estimated that 5%–10% of pancreatic cancers are hereditary and many inherited genetic disorders such as Lynch syndrome are reported to increase the risk of malignancy development [61]. Gene mutations related to PDAC include those in K-*ras*, occurring in more than 90% of human PDAC cases [67], as well as in *brca2* and *cdkn2a* [65].

Pancreatic endocrine tumours evolve from pancreatic endocrine tissue. NETs are very rare and account for 5% of all cases of pancreatic cancers [61]. NETs are classified according to the type of hormone they produce, that is, insulinoma (insulin), gastrinoma (gastrin), VIPoma (vasoactive intestinal peptide), and glucagonoma (glucagon) [68], and can serve as a basis for the development of other diseases. For example, insulinomas result in hypoglycemia, glucagonomas cause type I diabetes, and gastrinoma are associated with the Zollinger–Ellison syndrome. NETs are highly dependent on genetic factors, with a family history of sarcoma, gallbladder, ovarian or gastric cancers, or tuberous sclerosis, being predisposing factors to developing NETs. NET development is also associated with mutations in oncogenes such as *ccnd1* and *men1*, tumour suppressor genes *pRB*, *p53*, and the cyclin-dependent kinase inhibitor (CKI) p16INK4a, while a lesser role is played by environmental factors such as smoking or alcohol abuse [66].

4.1. Microbiota in Physiological Pancreas

The human pancreas has been reported to harbor its own microflora; however, little data have been obtained on this subject. It has been found that *Acinetobacter*, *Pseudomonas*, and *Propionibacterium* predominate in the microbiota of the healthy human pancreas; nevertheless, these data need further investigation owing to the limited size of the cohort used in the study (n = 7) [69].

4.2. Microbiota in Pancreatitis

Pancreatic adenocarcinoma has been described as an inflammation-driven cancer and clinical evidence suggests that bacteria are likely to influence the progression of pancreatitis by activating immune receptors and perpetuating cancer-associated inflammation [62]. Environmental stress factors can lead to the overgrowth of Gram-negative bacteria in the intestine. Altered gut microflora increases intestinal permeability, thus allowing pathogenic (Gram negative) bacteria to gain access to the bloodstream and reach distant organs such as the pancreas. Elevated systemic levels of LPS can also lead to chronic pancreatitis [62]. Jandhyala et al. reported a significant decrease in *Faecalibacterium prausnitzii* and *Ruminococcus bromii* in the gut microbiota of patients suffering from chronic pancreatitis. Both bacteria are important butyrate-producing commensals, while *Faecalibacterium prausnitzii* exhibits a wide range of beneficial effects on the host such as stimulation of the anti-inflammatory response, mucin synthesis, and tight-junction proteins in the gut, which improves gut barrier function [70]. Similarly, the gut microbiota of patients suffering from acute pancreatitis displayed higher levels of pathogenic *Enterococcus* bacteria with a significant decrease in the numbers of *Bifidobacterium* and Clostridium cluster XI, which are equally important butyrate producers [71].

The role of *Enterococcus faecalis* in cancer development remains unclear. It has been mostly reported as a gut commensal; however, owing to its wide range of virulence factors, especially its metalloprotease production and ability to generate ROS (reactive oxygen species) and extracellular superoxide, it has drawn attention as a carcinogenic [72]. ROS and extracellular superoxide lead to DNA damage, which might result in carcinogenic mutations. In addition, metalloprotease influences the gut epithelium, enhancing gut permeability and inducing inflammation [73]. The study of Boonanantanasarn et al. suggested that *E. faecalis* might enhance cell proliferation through hydrogen peroxide-mediated epidermal growth gactor receptor activation (EGFR). THE EGFR signalling pathway plays a crucial role in the regulation of cell proliferation in many cell types [72]. In contrast, Sivan et al. have reported that oral administration of *Bifidobacterium* to mice significantly increased anti-tumor immunity and improved tumor control on a comparable level to treatment with programmed cell death protein 1 ligand 1-specific antibodies [74].

Statistically, most often, pancreatitis development is driven by excessive alcohol consumption and the presence of gallstones. The third largest group includes pancreatitis of an unknown base. Both alcohol overuse and the presence of billiary stones influence host microbiota. Excessive alcohol consumption impairs intestinal wall integrity and was correlated with overgrowth of Gram-negative bacteria in the intestine. An increased amount of LPS with dysfunction of intestinal barrier can lead to systemic inflammation and, in a further perspective, influence pancreatitis development [62]. Ciocan et al. reported that intestinal microbiota of patients with alcoholic chronic pancreatitis (ACP) was enriched in pathogenic taxa such as *Klebsiella*, *Enterococcus*, and *Pseudomonas*, with a significant decrease in beneficial bacteria such as *Faecalibacterium prausnitzii* and *Ruminococcus bromii* from *Firmicutes phylum*. A study also reported that, overall, intestinal microbiota diversity in ACP patients was lower compared with healthy subjects [63]. Not much data are available, however, on microbiota changes in gallstone pancreatitits.

4.3. Microflora in Pancreatic Adenocarcinoma

While most gastrointestinal cancers are influenced by local microbiota, PDAC has been linked to dysbiosis in gut and oral microflora. Pushalkar et al. reported that the cancerous pancreas harbors a significantly different and more abundant gut microbiota compared with that of the normal pancreas in both mice and humans. The PDAC-related gut microbiota was found to be significantly enriched in Gram-negative Proteobacteria, Fusobacteria, Gram positive Actinobacteria, and Verrucomicrobia compared with healthy subjects. Even though these phyla are also abundant in healthy gut microbiota, their presence is modest compared with Firmicutes and Bacteroidetes [75,76]. Other studies reported that *Acinetobacter*, *Enterobacter*, *Pseudomonas*, *Delftia*, *Enterococcus*, *Streptococcus*, *Corynebacterium*, *Propionibacterium*, *Klebsiella*, *Sphingomonas*, and *Staphylococcus* are thought to be the

dominant bacterial genera in the gut microbiota of PDAC patients, with *Klebsiella* being the most abundant [75,76]. Increased *Klebsiella pneumoniae* abundance and K. Pneumoniae infection has been already reported in many cancers [77]. Pötgens et al. demonstrated on a murine model that *Klebsiella oxytoca* behaves as a gut pathobiont, that is, it increases gut permeability, and thus influences cancer progression [78]. Ren et al. demonstrated a significant decrease in commensal *Bifidobacterium* and butyrate-producing bacteria such as *Coprococcus*, *Clostridium* IV, *Blautia*, *Flavonifractor*, and *Anaerostipes* in PDAC patients [79]. These data suggest that enrichment in Gram-negative bacteria with a decrease in butyrate producers is positively correlated with pancreatic cancer development.

Moreover, the study of Thomas et al. reported that sole presence of microbiota in the gut as well as in the pancreas might accelerate PDAC development. A study suggest that $Kras^{G12D}/PTEN^{lox/+}$ mice with intact microbiota developped PDAC faster than mice lacking microflora after antibiotic treatment. They also point to the role of microbiome in immune system stimulation [69]. However, the study lacks data about specific bacterial taxa that might accelerate PDAC development. Interestingly, alterations in pancreatic and gut microbiota connected to PDAC in an animal model was found to result in both innate and adaptive immune suppression, which leads to faster cancer progression. It was suggested that translocation of Proteobacteria from gut to pancreas, which activates Toll-like receptors (TLRs) by bacterial lipopolysaccharides and flagellins, can promote tolerogenic macrophage phenotype in the tumour microenvironment [75]. The same study found that, while Proteobacteria were the most abundant phyla in both the gut and pancreatic microbiotas. Proteobacteria genera, that is, *Pseudomonas* and *Elizabethkingia*, were the most abundant in the pancreatic microbiota, and *Prevotella* and *Bacteroides* were more abundant in the gut [75].

PDAC development is also influenced by alterations in the oral microbiota. The human oral cavity harbors a complex microbial community known to contain over 700 species of bacteria, more than half of which have not been cultivated [80]. Even though oral microbiota can play a protective role against pancreatic cancer in a healthy, commensal state, it may also promote malignancy under pathologic conditions, especially while enriched in taxa related to periodontal disease [81,82]. Dysbiosis of oral bacteria resulting from poor oral hygiene, as well as associated diseases such as periodontitis and tooth loss, may promote bacterial translocation and increase the risk of pancreatic cancer [82]. A positive association between periodontal disease and pancreatic cancer has been observed; men reporting a positive history of periodontal disease showed a 64% higher risk of pancreatic cancer compared with those reporting no periodontal disease [83]. Since then, a number of studies have examined the correlation between oral microbiota and pancreatic cancer. The abundances of specific salivary bacteria, such as the ratio between *Leptotrichia* and *Porphyromonas* numbers, were believed to be useful biomarkers for early-stage pancreatic cancer; the oral microbiota of PDAC patients was reported to be enriched in *Leptotrichia* and poor in *Porphyromonas* and *Neisseria* [80]. *Leptotrichia* has been isolated from patients suffering from colorectal cancer, gastrointestinal ulcers, and systemic infections; however, its role in diseases is not clear [84]. Remarkably, antibodies to *Porphyromonas gingivalis* have been directly associated with pancreatic cancer development. Michaud et al. also suggested that a decrease in *Porphyromonas* in the oral microbiota of PDAC patients might result from an extensive immune response against those bacteria [83].

Porphyromonas gingivalis, *Tannerella forsythia*, and *Treponema denticola*, collectively called the red complex, are major pathogens responsible for chronic periodontitis. Those bacteria are believed to promote PDAC development via peptidylarginine deiminase secretion, which might lead to p53 and K-ras point mutations by degrading arginine [85]. Moreover, *A. actinomycetemcomitans*, another periodontal pathogen related to pancreatic cancer, was reported to initiate the Toll-like receptor signalling pathways. TLR activation has been shown to be tightly correlated to pancreatic carcinogenesis development in animal models [86]. Compared with healthy subjects, oral microbiota samples obtained from PDAC patients exhibited a significant decrease in commensal bacterial genera such as Fusobacteria *Corynebacterium*, as well as species such as *Neisseria elongata* and *Streptococcus mitis*, and an increased abundance of *A. actinomycetemcomitans* (aggressive periodontitis) and *Granulicatella*

adiacens (bacteremia and infective endocarditis), as well as *Leptotrichia*, whose number normally increases in cancer patients, and *Bacteroides* genus [84,86] (Table 4).

Table 4. Oral microbiota in pancreatic cancer. TRL, Toll-like receptor; PDAC, pancreatic ductal adenocarcinoma.

Bacteria	Carcinogenic Mechanism
P. gingivalis *T. forsythia* *T. denticola*	Degradation of arginine by bacterial peptidylarginine deiminase leading to *p53* and *K-ras* point mutations
P. gingivalis *A. actinomycetemcomitans*	TLR signaling pathways activation, which might lead to chronic inflammation and cancer in further perspective
N. elongata *S. mitis* *Porphyromonas* *Corynebacterium* *Aggregatibacter* *Fusobacteria*	Decreased abundance of commensal bacteria leads to oral microbiota dysbiosis and higher occurrence of oral pathogens
P. gingivalis *A. actinomycetemcomitans* *G. adiacens* *Leptotrichia* Bacteroides genus	Abundance of those pathogens tends to be higher in PDAC patient's oral microbiome, suggesting a potential role of those bacteria in PDAC carcinogenesis

Oral microbiota and its microbiome can influence pancreatic cancer development. Bacteria influence neoplastic changes by production of metabolites that lead to production of tumorigenic agents, induction of immune system, and displacement of commensal bacteria. Changes in gut microbiome composition are being reported in pancreatic cancer patients, however, the exact impact of dysbiosis in oral microbiome needs further investigation [84,86].

5. Liver Cancer

According to American Cancer Society statistics, about 42,030 new cases of primary liver cancer and intrahepatic bile duct cancer will be diagnosed among Americans in 2019 (29,480 in men and 12,550 in women), and about 31,780 people (21,600 men and 10,180 women) will die as a result of these malignancies [www.cancer.org]. These data are alarming as liver cancer incidence has more than tripled since 1980 [87].

Liver cancers are the third leading cause of worldwide cancer mortality. The vast majority (75–90%) of primary liver cancers are hepatocellular carcinomas (HCCs). Most liver cancers (83%) are diagnosed in less well-developed nations [88]. The development of HCC is strongly correlated with previous chronic liver disease characterized by an iterative cycle of liver damage, inflammation, and regeneration [53]. Risk factors for HCC include chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infection, as well as unhealthy lifestyle habits such as exposure to dietary aflatoxin, obesity, and smoking. Diseases such as diabetes, alcohol-induced cirrhosis, autoimmune primary biliary cirrhosis, and fatty liver disease also increase the risk of HCC development [88].

5.1. Gut Microbiota in Physiological Liver

As 70% of hepatic blood is delivered from the portal vein, it is constantly subjected to an inflow of intestinal toxins and microbial products. Under normal conditions, small amounts of bacteria or bacterial metabolites that enter the liver are eliminated by Kupffer cells without alarming the immune system. However, changes in intestinal microbiota composition can have a significant impact on liver condition. Research on the microbiota has exposed two microbiota-related axes in the human body:

interactions between the gut and the liver microbiota (liver–gut axis) and between the gut and the brain (gut–brain axis). The liver–gut axis is believed to be an important factor in the pathophysiology of liver diseases. Studies show that it might play an important role in non-alcoholic fatty liver disease and hepatic encephalopathy development [89].

5.2. Liver Cirrhosis-Related Microbiota

5.2.1. Primary Biliary Cirrhosis

Primary biliary cirrhosis (PBC) is an autoimmune disease affecting the small bile ducts. PBC outcome is related to alterations in genes encoding the human leukocyte antigen (HLA) system, IL-12 receptor, and TNF. PBC leads to progressive destruction of intrahepatic bile ducts, which results in cholestasis. This is alarming, because the main consequence of hepatic cholestasis is liver cirrhosis, a condition strongly connected with further cancer development [90,91]. It is believed that 95% of PBC patients produce antimitochondrial antibodies (AMAs) that target the pyruvate dehydrogenase complex E2 (PDC-E2) expressed by biliary epithelial cell. Those anti-PDC-E2 antibodies are considered as the main serological hallmark of PBC. Interestingly, several studies reported specific crosstalk between human PDC-E2 and gut microbiota; however, this phenomenon is not yet well defined. Antibodies to the ATP-dependent Clp protease of *E. coli* potentially mimics the T-cell epitope. Similarity between the β-galactosidase of *Lactobacillus delbrueckii* motif (BGAL LACDE) and the PDC-$E2_{212–226}$ motif SxGDL [ILV] AE is believed to result in the cross-talk between the anti-PDC-E2 antibodies of the hosts and the bacterial enzyme [91,92]. It has also been reported that mimicry of the *Novosphingobium aromaticivorans* PDC-E2-like proteins to pyruvate dehydrogenase can contribute to the outcome of PBC [93].

5.2.2. Liver Cirrhosis

Liver cirrhosis can be described as increased systemic liver inflammation. The main risk factor for liver cirrhosis development is chronic inflammation triggered by sepsis, endotoxemia, and other infections. Triggered immune system activates immune cells to produce disease-specific mediators. Mediators stimulate liver cells, that is, hepatocytes, hepatic stellate cells (HSCs), Kupffer cells, cholangiocytes, and hepatic T cells, to release inflammatory molecules, such as TNF, TGF-β1 (tumor growth factor Beta1), and IL-6. Those molecules activate HSCs to form myofibroblasts, the main effectors of fibrosis in all tissues. Myofibroblasts synthesize collagen, which, over time, results in the development of liver fibrosis and cirrhotic transformation [94,95]. In addition to liver inflammation and injury, cirrhosis outcome is also associated with a defective intestinal barrier, altered bile acids' (BAs) profile, and changes in gut microbiota [95].

Impairments in the intestinal barrier increase intestinal permeability, which enables bacterial products, such as endotoxins, peptidoglycans, and microbial DNA, to access and stimulate the intestinal immune system. Triggered inflammatory response increases the synthesis of potent cytokines such as IL-1, IL-6, IL-8, and TNF. Moreover, increased intestinal permeability enables bacteria and bacterial products to travel to the liver via the portal vein. Once in the liver, those bacterial products interact with the innate sensors (Toll-like receptors (TLRs) and NLRs) of hepatocytes and Kupffer cells, resulting in further production of inflammatory mediators and cirrhosis [94].

The microbiota of patients with liver cirrhosis differs from that of healthy patients [96]. This phenomenon is believed to be associated with Bas' synthesis in the human gut, as cirrhosis patients exhibit five times lower secretion of BAs in the intestine compared with healthy subjects [97]. It has been found that decreased BA secretion in the intestine might influence the composition of the gut microbiota as they are tightly connected. BAs regulate the composition of gut microbiota, and the microbiota of the small and large intestine contribute to bile acid synthesis by hydrolysing conjugated bile to free bile acids [98]. Reduced secretion of BAs during liver cirrhosis can lead to the overgrowth of harmful bacteria in the large intestine with simultaneous decrease of otherwise protective bacteria.

Alterations in gut microbiota lead to the translocation of immunogenic bacterial products, such as LPS or bacterial DNA, from the gut to liver. It has been found that patients with liver cirrhosis exhibit higher LPS levels. LPS is a strong endotoxin that can induce the inflammatory cascade by binding to receptors on many cells of the immune system. Excessive and persistent liver inflammation leads to repeated hepatocytic damage, hepatic fibrosis, cirrhosis, and finally HCC [91,99]. Additionally, BAs exhibit anti-inflammatory properties on intestinal epithelial cells; it has thus been proposed that reduction of BA secretion in the gut may additionally enhance chronic inflammation [91].

Yu et al., Chen et al., and Lu et al. reported that the gut microbiota in patients with liver cirrhosis showed a higher prevalence of pathogenic bacteria such as *Enterobacteriaceae*, *Streptococcaceae, Streptococcus*, and *Veilonella*, and a lower prevalence of beneficial bacteria such as Bifidobacteria, Bacteroidetes, Firmicutes, and Lachnospiraceae from the order *Clostridiales* compared with healthy controls [21,100–102]. *Veilonella parvula* has been reported to colonize different niches within the tumour [103], and has been associated with dental infections and inflammatory-related diseases such as osteomyelitis, meningitis [104], and prosthetic joint infection [105]. Those reports are based on a one-patient case study, and require confirmation on a larger study group. Members of the *Enterobacteriaceae* family were reported to exhibit direct cancerogenic activity on host cells. Those bacteria can induce hyperplasia by direct induction of the proliferation of epithelial cells. A study on human colonic cell lines found *Enterobacter* spp. proteins to considerably increase cell viability and proliferation and decrease cell apoptosis [106].

The *Lachnospiraceae* family includes commensal genera such as *Coprococcus*, *Pseudobutyrivibrio*, and *Roseburia*, which have a beneficial impact on host organism by short chain fatty acid production [101]. SCFAs exhibit a strong immune-modulating effect by being natural ligands for free fatty acid receptor 2 and 3 (FFAR 2/3). FFAR 2/3 are found on many cells, including immune system cells. SCFAs are also reported to have a beneficial effect on the host energy metabolism, by influencing glucose homeostasis through FFAR 2/3, and are known to affect lipid metabolism [107]. Moreover, SCFAs are important in the maintenance of gut integrity [101]. *Bifidobacteria* have also been reported to contribute to maintaining host health. Several studies have revealed the potential role of *Bifidobacteria* in colorectal cancer prevention and treatment. Bifidobacteria are believed to restrain cancer development by various mechanisms including oligosaccharide fermentation and biotransformation and by increasing the integrity of the intestinal barrier. Lactic fermentation is also suggested to have an antiproliferative effect on colorectal cancer cells, and lactic bacteria such as *Bifidobacterium* were reported to exhibit preventive effects against colon, bladder, liver, breast, and gastric cancer [108]. Moreover, the *Lactobacilli*, together with the *Bifidobacteria*, produce acetate and lactate. These acids influence the effects of SCFA-mediated prebiotics. Other SCFAs, butyrate and propionate, are produced by members of the Bacteroides phylum and the *Clostridium* clusters XIVa and IV [109].

5.3. Microbiota in HCC Liver Cancer

An increasing amount of data indicates that microbiota plays a key role in HCC development. A study on mice exposed to chemical carcinogens revealed that oral administration of probiotics (i.e., *Lactobacillus*, or combinations of *Streptococcus thermophilus* and *Bifidobacterium*) might slow down HCC development. It is believed that probiotics, by lowering serum LPS levels, enhance cancer development by alleviating chronic inflammation [103]. However, changes in gut microbiota composition are reported to promote HCC development. Research shows that gut microbiota of patients with advanced liver disease and cirrhosis are characterized by an increase in potentially pathogenic bacteria such as *Proteobacteria*, while the number of bacteria with beneficial properties is significantly reduced. This increased prevalence of pathogenic bacteria in the gut microbiota is associated with secretion of specific microbe-associated molecular patterns and substances. Combined with the excessive immune response triggered by microbial antigens, these harmful metabolites might lead to the development of liver fibrosis and genotoxicity [99,102].

It is well known that alcohol abuse is one of main causes of liver cirhossis and cancer development. It is worth noticing that excessive alcohol consumption significantly influences the intestinal community of microbes. Dubinkina et al. reported that the intestinal microbiome of patients with alcoholic liver disease (ALD) had decreased a number of members of Bacteroidales order, which are important butyrate-producing bacteria, as well as depletion in *Parabacyeroides* genus, *Prevotella*, and *Clostridium*. Moreover, ALD-related microbiome was enriched in oral microbes (such as *Streptococcus constellatus*, *S. salivarius*, *Veillonella atypica*, *V. dispar*, and *V. parvula*) and, interestingly, *L. antri*, *crispatus*, *delbrueckii*, *oris*, *ultunensis*, and *B. animalis* and *dentium*: members of *Lactobacillus* and *Bifidobacterium genera* [110].

Moreover, it is believed that microbiota may influence HCC progression by contributing to the progression of viral hepatitis, one of the common causes of HCC development. Sandler et al. indicate a correlation between microbial translocation and the degree of liver disease in patients with chronic viral HBV or HCV infection [111]. An in vivo study conducted on mice with viral-induced liver disease found that germ-free mice were protected from HCC development in comparison with controls. These data suggest that HBV and HCV infection might promote HCC development in a microbiota-related manner [112].

HCC patients display a different gut microbiota composition to healthy subjects. Until now, most data report that changes in HCC-related microbiome comprise a decrease in beneficial bacteria taxa such as Lachnospiraceae, Ruminococcacear, and Clostridiales, and an increase in Enterobacteriaceae and Bacteriodaceae [113]. Yu et al. reported a significant increase of Gram-negative bacterial strains in a mouse model of cirrhosis HCC [102] (murine model, immunochemistry). Pinero et al. reported that HCC-related gut microbiota differed from wo-HCC by different abundance of Firmicutes phylum (with an increase in *Erysipelotrichaceae* and decrease in *Leuconostocaceae* families), a decrease in Fusobacterium genus, and an increased ratio of bacteroides/prevotella [113]. It is being suggested that increased levels of circulating LPS and impairment of gut barrier integrity influence cancer develpment. High circulating levels of LPS have been noted in both animal models of carcinogen-induced hepatocarcinogenesis and HCC patients [5,102]. An elevated LPS level is frequently associated with intestinal permeability and bacterial translocation and can cause pro-inflammatory activity in the liver [114]. Diet is also an important agent in hepatocarcinogenesis. Yoshimoto et al. reported that dietary or genetic obesity leads to changes in gut microbiota composition, leading to an increase of deoxycholic acid (DCA) production. The gut microbiota involved in bile acid metabolism also influence DCA synthesis. High levels of DCA in the blood and feces are associated with an elevated risk of cholesterol gallstone disease and colon and liver cancer, as DCA is reported to damage DNA and induce production of various inflammatory and tumor-promoting factors in the liver [114] (Table 5).

Changes in gut microbiota in HCC patients are characterized by a decrease in commensal bacteria and butyrate producers with an increase in pathogenic bacteria that contribute in the development of inflammation. Moreover, bacteria such as *Clostridium scindens*, *C. hylemnoae*, and *Eubacterium* produce 7α-dehydroxylase, which mediates transformation of primary bile acids into deoxycholic acids, reported to cause DNA damage.

Faecal samples from 92 patients and 32 healthy controls; results obtained by quantitative PCR and immunological techniques [100]; review [101] mouse model, immunochemistry [102]; 16 patients with minimal fibrosis, 68 with cirrhosis, and 67 uninfected volunteers [111]; Analysis of human plasma levels of lipopolysaccharide (LPS) by the limulus amebocyte lysate assay, at presentation and after antiviral treatment.

Table 5. Impact of gut microbiota on liver cancer. HBV, hepatitis B virus; HCV, hepatitis C virus; HCC, hepatocellular carcinoma.

Mechanism	Bacteria	Description	Reference
Contribution to the progression of viral hepatitis	Increase in *Veilonella* and *Streptococcus* spp. in gut microbiota. Decrease in *Bifidobacteria*, *Bacteroides*, *Firmicutes*, *Lachnospiraceae*, and *Clostridiales.*	Chronic infection with HBV or HCV leads to liver cirrhosis. It was reported that liver cirrhosis alters gut bacteria. Microbiota imbalance leads to inflammatory cascade that might result in HCC.	[21,100–102,111]
Production of harmful bacterial metabolites	*Clostridium scindens*, *C. hylemnoae*, and *Eubacterium*	Bacteria such as *Clostridium scindens*, *C. hylemnoae*, and *Eubacterium* produce 7α-dehydroxylase, which mediates transformation of primary bile acids into deoxycholic acids, reported to cause DNA damage.	[115]
Decrease of butyrate producing commensal bacteria	Increase in *Eschericha*, *Atopobium*, and *Clostridia* with decrease in *Enterococcus*, *Lactobacillus*, and *Bifidobacterium.*	Changes in gut microbiota in HCC patients are characterized by decrease in commensal bacteria and butyrate producers with increase in pathogenic bacteria that contribute in the development of inflammation.	[99,100,102]

6. Biliary Tract Cancers

Biliary tract cancers (BTCs) encompass a heterogeneous group of carcinomas arising from the cholangiocytes, that is, epithelial cells of the bile ducts. BTCs include extrahepatic cholangiocarcinoma (EHCC), intrahepatic cholangiocarcinoma (IHCC), gallbladder cancer, and ampullary carcinoma [116,117]. BTCs are relatively rare, with about 10,000 new cases and 3000 deaths being reported each year in the USA. However, those tumours are reported as highly fatal. Owing to their strong heterogeneity, BTCs are difficult to diagnose and treat and the five-year overall survival for patients with biliary tract cancers only approaches 15% [118]. Genomic aberrations are common within BTC, and they share mutations in cell cycle regulators (specifically *cdkn2b*) and chromatin remodelling (*arid1a*). Mutations in IHCC encompass *fgfr* fusions, substitutions in *braf* and *idh1/2* substitutions, *met* amplifications, and a low mutational frequency in *K-ras*. Common mutations in EHCC and gallbladder tumors comprise amplification of *Erbb2* and aberrations in the the phosphatidylinositol-3-kinase (PI3K)/AKT/mechanistic target of rapamycin (MTOR) pathway [116]. Gastrointestinal diseases such as gallstone disease, asymptomatic stone disease, obesity, and diabetes mellitus, as well as chronic inflammatory states, such as primary sclerosing cholangitis, are also strong risk factors for BTC development. Furthermore, chronic biliary tract infections caused by bacteria (i.e., *Salmonella typhi*, *Helicobacter bilis*), parasites (i.e., *Opisthorchis viverrini*, *Clonorchis sinensis*), or viruses (hepatitis B virus and hepatitis C virus) are believed to potentially lead to BTC development [117].

6.1. Gallbladder Cancer

Cancer of the gallbladder is the most common cancer of the biliary tract, constituting 80% to 95% of cancers of the bile ducts. American Cancer Society statistics predicts that, in 2019, about 5000 new cases of gallbladder cancer will be diagnosed in United States and approximately 1500 fatalities will occur [www.cancer.org]. The disease develops over 5 to 15 years during a process of progressive transformation. Metaplastic changes lead to dysplasia, followed by carcinoma in situ, and finally invasive gallbladder cancer [119]. Gallbladder cancer is often reported as fatal owing to its silent progression and difficulties in diagnosis. It has an overall mean survival rate of six months and a five-year survival rate of 5% [119,120]. Obesity, female sex, older age, and family history are strongly linked with malignancy development. Diseases such as gallstone disease, primary sclerosing cholangitis, and chronic inflammation might also result in cancer development. Moreover, bacterial, parasite, and viral infections have also been linked with gallbladder malignancy [119].

6.2. Ampullary Cancers

Ampullary cancers are rare malignancies accounting for only 0.2% of GI cancers. Ampullary cancers arise from the transformation of the ampulla of Vater and are reported to be less aggressive and to have better prognosis after therapy than cancer of the distal bile duct or the pancreas [121,122]. Ampullary cancers are a heterogenous group and, depending on their epithelium of origin ampullary cancers, were split into subtypes: intestinal-type ampullary adenocarcinoma originating from the intestinal epithelium overlying the ampulla and pancreaticobiliary-type arising from the epithelium of the distal pancreatic duct and distal common bile duct [122]. No evident risk factors are reported to promote ampullary carcinoma development. However, attention is paid to the role of age, hypertension, diabetes, cholelithiasis, cholecystectomy, and chronic pancreatitis [123,124].

6.3. Microbiota in BTC

Given the fact that bile acids exhibit strong antimicrobial properties, the biliary tract was assumed to be a germ-free environment. However, a study of patients with acute cholangitis or cholecystitis reported occurrence of bacteria in their biliary tracts [91]. It has also been found that microbiota composition can influence BTC development by altering bile acid signaling [125].

Unfortunately, not much data concerning microbiome are available for biliary tract cancer. The first study of BTC-related microbiota and microbiota was conducted by Avilés-Jiménez et al. in 2015 to characterize the differences in the microbiota in the biliary tract of patients with BTC and those with benign biliary pathology (BBP). Studies on the microbiota of patients with BTC and BBP reported that bile tract microbiota differs between two study groups. BTC patients' microbiota was enriched in *Fusobacterium*, *Prevotella*, *Helicobacter*, *Campylobacter*, *Methylophiliaceae*, *Sinobacteriaceae*, *Actinomyces*, *Dialister*, and *Novosphingobum*, with significant abundance of *Fusobacterium*, *Prevotella*, *Helicobacter*, and *Campylobacter*. BPP microbiota was less abundant and differentiated from BTC microbiota, with *Nesternkonia*, *Rothia*, and *Mesorhizobium* being the most abundant species [126] (Table 6). *Rothia* is a part of the commensal oral microbiota. *Novosphingobium* has already been linked to primary liver cirrhosis and cancer. It has been reported that the bacterium induces an autoimmune response in the host organism owing to the similarity between its PDC-E2-like proteins and human pyruvate dehydrogenase [93]. *Methylophilaceae* and *Nesterenkonia* have been mostly isolated from soil and lake sediments, and *Mesorhizobium* exists in symbiosis with plant roots and has been rarely isolated from humans [126,127]. Other studies suggest that infection with *Helicobacter* species may represent a risk for BTC as *H. bilis* and *H. hepaticus* were reported to increase the chance of biliary tract and gallbladder cancer development [127,128].

Table 6. Differences in most abundant bacteria species in bile tract microbiota composition isolated from biliary tract cancer (BTC) patients and patients with benign biliary pathology (BBP) (distribution of clones at the genus level).

BTC	BBP
Fusobacterium↑	
Prevotella↑	
Helicobacter	
Campylobacter ↑	*Nesterenkonia*
Methylophilaceae	*Rothia*
Sinobacteriaceae	*Mesorhizobium*
Actinomyces	
Dialister	
Novosphingobium	

Studies on the microbiome of patients with BTC and BPP reported that bile tract microbiota differs between two study groups [126–129].

Bile samples from 125 patients with various hepato-biliary diseases: 75 with biliary stones, 15 with pancreatico-biliary malignancies, and 4 with primary sclerosing cholangitis. 16S Illumina sequencing [126]; review article [127]; bile samples from from 125 patients with various hepatobiliary diseases: 75 with biliary stones, 15 with pancreatico-biliary malignancies, and 4 with primary sclerosing cholangitis, Helicobacter genus-specific primers [128]; 22 gallbladder and liver biopsy specimens. Helicobacter genus-specific 16S rDNA PCR [129].

Chronic *Salmonella* enterica serovar Typhi infection has also been reported to be associated with a significant risk of gallbladder cancer development. Scanu et al. has shown on an animal model that chronic infection with *Salmonella typhi* encourages malignant transformation in predisposed mice. Scanu et al. have reported that *Salmonella* infection enhances activation of mitogen-activated protein kinases (MAPK) and protein Kinase B (AKT) pathways; this can suggest a possible mechanism by which the bacteria influence cancer development, as upregulation of MPK and AKT pathways is frequently observed in human cancers. *Salmonella* produces about 40 proteins that enable the pathogen to infect host cells. Bacterial proteins SopB, SopE, and SopE2 promote *Salmonella* uptake by host cells via the initiation of the host MAPK pathway. In addition, SopB protein, secreted in order to prevent fusion of the Salmonella-containing vacuole with lysosomes, also triggers the host MAPK pathway [130].

7. Colorectal Cancer

Colorectal cancer (CRC) is the third most common cancer in both men and women, and the most frequent malignancy of the gastrointestinal tract [131]. The American Cancer Society predicts that, in 2019, 101,420 new cases of colon cancer and 44,180 new cases of rectal cancer will be diagnosed, and 51,020 CRC patients will die (www.cancer.org). Most (>90%) CRCs are adenocarcinomas. Other types, such as neuroendocrine, squamous cell, adenosquamous, spindle cell, and undifferentiated carcinomas, are very rare [132]. In this article, we will focus only on colorectal adenocarcinomas.

Age is a major risk factor for sporadic CRC. The risk of developing a malignancy increases significantly after 50 years of age [131]. Moreover, genetic factors are an important player in CRC development. Autosomal inherited syndromes such as familial adenomatous polyposis (FAP) and Lynch syndrome (hereditary nonpolyposis colorectal cancer; HNPCC) are associated with a higher risk of CRC development (approximately 5% of CRC cases). About 10% of CRC cases result from pathogenic mutations that are not associated with HNPCC or FAP; most are mutations in genes with high penetrance, such as *apc*, *mutyh*, brca1/2, *palb2*, cdkn2a, and *tp53*, and those of moderate penetrance, such as *mutyh*, *apc* allele p.I1307K, and *chek2* [131,133]. Additionally, several gastrointestinal diseases are reported to increase the risk of CRC outcome. Ulcerative colitis and Crohn's disease increase the risk of CRC by about 15%. Cystic fibrosis, diabetes, and insulin resistance are also related to CRC [134].

Although genetic factors play an important role in CRC development, most colorectal malignancies are more sporadic than familiar. CRC is 25% more common among men than women. Low socioeconomic status, physical inactivity, and an unhealthy diet (especially extensive consumption of red and processed meat, as well as a high-calorie, fat-rich, and fibre-deficient diet) all increase the risk of CRC development, as well as smoking, alcohol consumption, and obesity [131,134]. Moreover, several bacterial and viral agents such as John Cunningham virus, human papillomavirus, *Streptococcus bovis*, *Helicobacter pylori*, *Fusobacterium*, pathogenic strains of *E. coli*, and decreased diversity of commensal microbes in the gut have been proposed as risk factors for CRC [134].

7.1. Microbiota in Physiological Gut

Even though gut microbiota composition is influenced by a variety of factors including diet, stress, or drug intake, its general profile remains relatively constant. A physiological gut microbiota is dominated by the strict anaerobes *Eubacterium*, *Fusobacterium*, *Bacteroides*, *Bifidobacterium*, *Atopobium*, and *Peptostreptococcus*, and facultative aerobes *Lactobacilli*, *Enterococci*, *Enterobacteriaceae*, and *Streptococci* [70,135] (Human Microbiome Project; https://hmpdacc.org/hmp/). This specific composition of gut microflora positively influences gut homeostasis and prevents gut colonisation by pathogenic bacteria [70,135]. The commensal gut microbiota is also inhabited by primary pathogens such as *Campylobacter jejuni*, *Salmonella enterica*, *Escherichia coli*, *Bacteroides fragilis*, and *Vibrio cholera*; however, their abundance is scarce, constituting <0.1% of the whole microbiota. In addition, healthy gut microbiota are characterized by a low abundance of Proteobacteria with simultaneous enrichment of *Bacteroides*, *Prevotella*, and *Ruminococcus* genera [70].

7.2. Microbiota in Colorectal Cancer

The main mechanism by which the gut microbiota can influence CRC development is the release of inflammatory agents, which promote the change of normal cells to cancerous mutants [135]. Flemer et al. reported that the Firmicutes Cluster 1, being important SCFA producers, as well as the Bacteroidetes Cluster 1, were significantly less abundant in CRC biopsy microbiota than healthy controls; in addition, Firmicutes and Bacteroidetes phyla as well as *Prevotella* genera were more abundant [136]. Other studies have found *Roseburia*, *Ruminococcus*, *Oscillibacter*, *Fusobacterium* (especially *F. nucleatum* and *F. varium*), and *Porphyromonas* to be more abundant in the faecal samples of CRC patients then controls, as well as Bacteroides and *Prevotella* (*P. stercorea*). Cong et al. reported that the microbiota of CRC patients was significantly less diverse than that of healthy subjects (alpha diversity analysed by richness, phylogenetic diversity, Shannon diversity, and Simpson diversity), and that CRC patient microbiota was richer in members of *Clostridium XlVa*, *Fusobacterium*, *Parvimonas*, and *Peptostreptococcus* genera. They also note that the presence of *Fusobacterium* bacteria was significantly associated with lymphatic invasion of cancer cells ($p < 0.05$) [136].

In addition, Flemer et al. reported that the cancer microbiota varies depending on the placement of the CRC. *Alistipes*, *Akkermansia*, *Halomonas*, and *Shewanella* numbers were significantly higher in individuals with rectal and distal cancers, while *Faecalibacterium*, *Blautia*, and *Clostridium* were more abundant in individuals with proximal cancer [136] (Table 7).

CRC patients' microbiota undergoes specific rearrangement. Abundance of Firmicutes and Bacteroidetes, reported as the commensal gut microbiota, is significantly decreased, while species that are not common or rare in gut microbiota are increasing. Faecal and mucosal samples from 42 CRC cases and 89 matched controls. 16S sequencing [136]; faecal and mucosal samples from 59 patients undergoing surgery for CRC, 21 individuals with polyps, and 56 healthy controls. 16S rRNA amplicon sequencing, qPCR. Metabolomics analyses, that is, high-performance liquid phase chromatography and gas chromatography coupled with tandem mass spectrometry [137]; faecal samples from 203 colorectal cancer and 236 healthy subjects. Probe-based duplex quantitative PCR (qPCR) assays [138]; faecal samples from 10 CRC patients and 11 healthy controls. 16S rRNA amplicon sequencing [139].

Table 7. Changes in colorectal cancer (CRC) patients' microbiome compared with healthy subjects (distribution of clones at the phylum, genus, and species levels).

Increasing Bacteria	Decreasing Bacteria
Firmicutes	
Cluster	
Prevotella	
Cluster	
Bacteroidetes Cluster 2	
Roseburia	
Ruminococcus	
Oscillibacter	
Fusobacterium	
Porphyromonas	
Prevotella	Firmicutes Cluster 1
Bacteroides fragilis	Bacteroidetes Cluster 1
Clostridium nexile	
Actinomyces odontolyticus	
Haemophilus parainfluenzae	
Streptococcus gordonii	
Veillonella dispar	
Clostridium septicum	
Enterococcus faecalis	
Streptococcus bovis	
Helicobacter pylori	
Escherichia coli	

Abbreviation: CRC—colorectal cancer.

Several studies have reported that certain bacteria appear to be directly associated with the pathogenesis of colorectal cancer, and bacterial species such as *Enterococcus faecalis*, *Bacteroides fragilis*, *Streptococcus bovis*, *Helicobacter pylori*, *Fusobacterium* spp., and *Escherichia* coli have been reported to significantly influence the development of CRC [135,136]. Wu et al. note that *Bacteroides fragilis* is able to induce colitis and colonic tumors in an $Apc^{Min/+}$ mice model by activating a lymphocytes T helper type 17 (Th17) inflammatory response [54]. Significant enrichment in *Fusobacterium* spp. has already been reported in samples from colorectal patients in multiple studies [138,139]. Moreover, studies show that the oral pathogen *F. nucleatum* adheres to colonic epithelial cells through its FadA (*Fusobacterium nucleatum* adhesion protein) adhesion protein. FadA activates β-catenin signaling by binding to E-cadherin in colonic cells, which deregulates inflammatory and oncogenic responses [135,140]. Several researchers have also shown that a high-abundance of *F. nucleatum* induces a series of specific tumour molecular events, including CpG island methylator phenotype; microsatellite instability; and genetic mutations in *braf*, *chd7*, *chd8*, and *tp53* [140]. *Enterococcus faecalis*, repeatedly found in CRC patients, produces reactive oxygen and nitrogen species that directly lead to DNA breaks, point mutation, and chromosomal instability [73]. Even though *H. pylori* is mostly recognized with stomach cancer, the bacterial cytotoxin-associated gene A (CagA) and vacuolating cytotoxin gene A (VacA) encoded in some *H. pylori* strains might play a role in the primary phase of colorectal carcinogenesis owing to their potential to induce inflammation pathway activation. However, data being published on potential *H. pylori* correlation with CRC development are not consistent and vary between research groups [141]. Most *E. coli* isolated from CRC patients harbor the *pks* genomic island, which is responsible for the synthesis of colibactin. Colibactin is another bacterial-derived genotoxin that can interfere with the cell cycle and promote proliferation of epithelial cells via DNA damage, mutation, and genomic instability [142].

S. bovis infection has been reported to influence colorectal cancer formation by inducing a strong immune response, directly influencing unrestrained cellular proliferation and altering the composition of gut microflora [143]. Ellmerich et al. reported that administration of *S. bovis* or its antigens leads to the development of preneoplastic lesions in the colonic mucosa in a rat model; the bacterium influenced

tumour progression by increasing the expression of proliferation markers, boosting the production of highly immunostimulant IL-8, TNF-α, IL-1β, and IL-6, and enhancing formation of hyperproliferative abnormal colonic crypts [144]. *S. bovis* is also believed to impact the composition of gut microbiota by influencing the hepatic secretion of bile salts. Zarkin et al. reported that 56% of patients undergoing *S. bovis* bacteraemia suffered from hepatic dysfunction [145]. In addition, Caco-2 (human epithelial colorectal adenocarcinoma cells) cells, in the presence of *S. bovis* proteins, demonstrated significantly upregulated phosphorylation of MAPK [146]. The uncontrolled upregulation of signalling pathways induced by extensive phosphorylation of MAPK has been reported to be implicated in the development of many types of cancer [147].

8. Conclusions

Gastrointestinal cancers, that is, esophageal, stomach, liver, biliary tract, pancreas, and colon cancers, account for one-third of total cancer incidence and mortality in developing countries. Commensal microbiota is believed to have a beneficial influence on human health; however, numbers of studies aim to demonstrate if changes in gut microbiota contribute to the pathogenesis of gastrointestinal malignancies. A lot of interest is set on the link between microbiota and cancer. Microbiota is believed to contribute to cancer development through various mechanisms, such as (a) tissue homeostasis disruption through over amplification of the immune response, (b) activation of epithelial proliferation, and (c) breakdown of the integrity of the barrier.

In this review article, we have illustated microbial signatures in GI cancers (Table 8). It is worth noticing that few phyla are common for almost all GI malignancies. An increase in members of Proteobacteria, Acinetobacteria, and Fusobacteria phyla in gut microbiota was reported in almost all GI cancers. Proteobacteria has been linked to various human diseases, especially inflammation-related [148]. Studies reveal that impairments in the innate immune system promote the outgrowth of Proteobacteria, and that increases in the Proteobacteria number enhance the immune response in the host gut, which might lead to systemic inflammation development [57,58]. Members of Acinetobacteria phylum are opportunistic pathogens. A direct link between Acinetobacteria phyla with cancer development was not reported, however, infections with these bacteria are common among cancer patients [149,150]. Members of Fusobacteria phylum were reported to be related to GI cancer development. *F. nucleatum* has been suggested by a considerable number of studies as a potential marker for CRC detection [150]. *Leptotrichia* spp. infections are common among cancer patients [151].

Certain strains of *Escherichia coli*, *Streptococcus bovis*, *Helicobacter pylori*, *Bacteroides fragilis*, and *Enterococcus* spp., as well as some members of the *Enterobacteriaceae* family, were reported to exhibit direct cancerogenic activity on host cells. Those strains, by direct induction of proliferation of epithelial cells, can lead to hyperplasia. Moreover, changes in gastrointestinal microbiota are reported to occur in various gastrointestinal cancers. Nonetheless, despite the ever-increasing amount of data on human microbiome, there are still questions lacking answers. Why microbiota undergo changes in cancer environment? Are changes in microbiota diversity a cause or a result of cancer neoplastic transformation? Do changes in microbiota community increase or enhance cancer development? Answers to those questions might provide more information about the relation between cancer and host microbiota. An obstacle in the complete analysis of microbiota composition is also a huge number of bacterial genomes that could not be recognized and still fall into the dark matter. Moreover, all studies that were quoted in this review article present data obtained by 16s sequencing, while this method is cheap and provides enough information about taxonomic diversity of microbiota, it lacks data about metabolic changes occurring in the microbial community, which is also crucial. Furthermore, it is also crucial to include environmental factors into statistical analysis in order to evaluate the authentic role of microbiota in GI cancer development.

Table 8. Microbial signature of gastrointestinal cancers.

Cancer	Increased Bacteria Comparing to Healthy Subjects
Esophagus cancer	*Treponema denticola, Streptococcus mitis, Streptococcus anginosus* [18] *Fusobacterium nucleatum* [3] *Porphyromonas, Fusobacterium nucleatum* [30]
Gastric cancer	Proteobacteria (*Xanthomonadaceae* and *Enterobacteriaceae*, as well as genera such as *Citrobacter*, *Phyllobacterium* and *Achromobacte*), Firmicutes (*Lactobacillus, Clostridium*), Bacteroidetes, Actinobacteria (*Rhodococcus)* and Fusobacteria [44,49,50] oral bacteria (*Peptostreptococcus*, *Streptococcus*, and *Fusobacterium*) [52] bacteria harbouring nitrosating enzymes [51,52]
Pancreatic cancer	*Acinetobacter, Enterobacter, Pseudomonas, Delftia, Enterococcus, Streptococcus, Corynebacterium, Propionibacterium, Klebsiella, Sphingomonas, Staphylococcus* [75,76] *Klebsiella oxytoca* [78]
Liver cancer	Proteobacteria [99] *Erysipelotrichaceae, increased ratio bacteroides/prevotella* [102] *Veillonella, Streptococcus* spp. [100]
Biliary tract cancers	*Fusobacterium, Prevotella, Helicobacter, Campylobacter, Methylophiliaceae, Sinobacteriaceae, Actinomyces, Dialister, Novosphingobum* [126] *billiary tract mcirobiota
Colorectal cancer	Firmicutes, Bacteroidetes (*Prevotella*) [136] *Roseburia*, *Ruminococcus*, *Oscillibacter*, *Fusobacterium* (especially *F. nucleatum* and *F. varium*), *Porphyromonas, Parvimonas, Peptostreptococcus* [137]

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Abbreviations

AMAs—antimitochondrial antibodies, BAs—bile acids, BBP—benign biliary pathology, BE—Barrett's esophagus, BFT—*B. fragilis* toxin, BTC—biliary tract cancers, CagA—cytotoxin-associated gene A, CFU—colony-forming units, CRC—colorectal cancer, DCA—deoxycholic acid, EC—esophageal cancer, EHCC—extrahepatic cholangiocarcinoma IHCC—intrahepatic cholangiocarcinoma, ESCC—esophagus squamous cell carcinoma, FadA—fusobacterium nucleatum adhesion protein, FAP—familial adenomatous polyposis, FFAR 2/3—free fatty acid receptor 2 and 3, GC—gastric cancer, GERD—gastroesophageal reflux disease, GROα—growth-regulated protein α, HBV—hepatitis B virus, HCCs—hepatocellular carcinomas, HCV—hepatitis C virus, HDGC—hereditary diffuse gastric cancer, HLA—human leukocyte antigen, HNPCC—hereditary nonpolyposis colorectal cancer, HPV—human papilloma virus, HSCs—hepatic stellate cells, IF—intestinal flora, LPS—lipopolysaccharide, MMP-9—matrix Metalloproteinase-9, NAFLD—nonalcoholic fatty liver disease, NETs—named pancreatic neuroendocrine tumors, PBC—primary biliary cirrhosis, PDAC—pancreatic ductal adenocarcinoma, PDC-E2—pyruvate dehydrogenase complex E2, ROS—reactive oxygen species, SCFA—short chain fatty acids, Td-CTLP—chymotrypsin-like proteinase, Th17—lymphocytes T helper type 17, TLR—Toll-like receptor, TNF-α—tumor necrosis factor, VacA—vacuolating cytotoxin gene A.

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