The Role of Microbiota in Gastrointestinal Cancer and Cancer Treatment: Chance or Curse?

Annemieke Smet,1,2 Juozas Kupcinskas,3 Alexander Link,4 Georgina L. Hold,5,§ and Jan Bornschein6,§

1Laboratory of Experimental Medicine and Paediatrics, Faculty of Medicine and Health Sciences, 2Infla-Med Research Consortium of Excellence, University of Antwerp, Antwerp, Belgium, 3Institute for Digestive Research, Department of Gastroenterology, Lithuanian University of Health Sciences, Kaunas, Lithuania, 4Department of Gastroenterology, Hepatology and Infectious Diseases, Otto-von-Guericke University, Magdeburg, Germany, 5Microbiome Research Centre, St George and Sutherland Clinical School, University of New South Wales, Sydney, Australia, and 6 Translational Gastroenterology Unit, Nuffield Department of Experimental Medicine, University of Oxford, John Radcliffe Hospital, Oxford, United Kingdom

SUMMARY

With the widely accepted concept that human health is shaped by microbes, we present an overview of the involvement of microbiota in gastrointestinal cancer biology. This includes mechanistic insights as well as the impact on diagnostics and cancer treatment.

The gastrointestinal (GI) tract is home to a complex and dynamic community of microorganisms, comprising bacteria, archaea, viruses, yeast, and fungi. It is widely accepted that human health is shaped by these microbes and their collective microbial genome. This so-called second genome plays an important role in normal functioning of the host, contributing to processes involved in metabolism and immune modulation. Furthermore, the gut microbiota also is capable of generating energy and nutrients (eg, short-chain fatty acids and vitamins) that are otherwise inaccessible to the host and are essential for mucosal barrier homeostasis. In recent years, numerous studies have pointed toward microbial dysbiosis as a key driver in many GI conditions, including cancers. However, comprehensive mechanistic insights on how collectively gut microbes influence carcinogenesis remain limited. In addition to their role in carcinogenesis, the gut microbiota now has been shown to play a key role in influencing clinical outcomes to cancer immunotherapy, making them valuable targets in the treatment of cancer. It also is becoming apparent that, besides the gut microbiota’s impact on therapeutic outcomes, cancer treatment may in turn influence GI microbiota composition. This review provides a comprehensive overview of microbial dysbiosis in GI cancers, specifically esophageal, gastric, and colorectal cancers, potential mechanisms of microbiota in carcinogenesis, and their implications in diagnostics and cancer treatment. (Cell Mol Gastroenterol Hepatol 2022;13:857–874; https://doi.org/10.1016/j.jcmgh.2021.08.013)

Keywords: Gastrointestinal Cancer; Gut Microbiota; Diagnostics; Therapeutics.

The gut microbiota has arguably become one of the most exciting frontiers in health in the past decade. Since the development of next-generation sequencing technologies and their application within clinical research, our understanding of the human microbiome and its role in health and disease has increased exponentially.1,2 The influence of the gut microbiota, which consists of trillions of bacteria along with fungi, archaea, and viruses, extends to other body compartments including the liver, brain, and immune system, and alterations in gut microbiota have been reported consistently in various pathologic conditions. In addition, there is increasing appreciation of the gut microbiota’s contribution to cancer development,3 with 15%–20% of cancers known to be driven by specific infectious agents,4 while other malignancies are linked to the collective gut microbiota with/without involvement of specific trigger organisms.5–7 Microbiota influence on cancer risk is multifactorial, impacting host metabolism, immune function, host/microbial sensing pathways, and cellular proliferation.6 For instance, carbohydrate structures, which are present on gastrointestinal mucins, act as binding sites and/or metabolic substrates for bacteria and are important determinants in site-specific microbial colonization.5

Microbiologically induced chronic inflammation is a key risk factor in cancer initiation/progression with processes, including metastasis and tumor invasion, being accelerated as a result.5–7 Microbiologically induced pro-inflammatory cytokine level increases can lead to epithelial DNA damage.8

Abbreviations used in this paper: CRC, colorectal cancer; EAC, esophageal adenocarcinoma; ESCC, esophageal squamous cell carcinoma; ETBF, enterotoxigenic Bacteroides fragilis; FMT, fecal microbiota transplantation; GC, gastric cancer; GERD, gastroesophageal reflux disease; GI, gastrointestinal; HFD, high-fat diet; ICI, immune checkpoint inhibitor; PD-1, programmed cell death 1; PPI, proton pump inhibitor; RID, radiotherapy-induced diarrhea; Th, T-helper cell; TLR, Toll-like receptor.

© 2021 The Authors. Published by Elsevier Inc. on behalf of the AGA Institute. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
including epigenetic regulatory changes, which in turn induce genetic instability. These factors influence cancer initiation, promotion, dissemination, and also impact treatment.

In this review, we explore the contribution of gut microbes in esophageal, gastric, and colorectal cancers. We also offer a glimpse toward future developments in relation to microbial manipulation strategies in the context of cancer prevention and management.

**Esophageal Cancer**

Esophageal cancer is a major cause of global cancer mortality, with 2 distinct histologic types (ie, esophageal squamous cell carcinoma [ESCC] and esophageal adenocarcinoma [EAC]). Globally, ESCC incidence is decreasing whereas a rapid increase in EAC cases has been seen alongside a widespread adoption of a Western diet and an increase in obesity, both factors contributing to gastro-esophageal reflux disease (GERD), the main risk factor for EAC. In most cases, EAC is preceded by its precancerous lesion, Barrett esophagus (BE). Several studies have assessed microbiota signatures in esophageal carcinogenesis (Supplementary Table 1), with microbiota composition mostly being assessed in tissue specimens or oral mucosal swabs, with no significant differences in biopsy and oral swab microbial signatures seen. Overall, decreased species diversity/richness is seen in ESCC, EAC, and BE compared with normal esophageal tissue (Supplementary Table 1). Genera that are more consistently enriched in BE include *Campylobacter*, *Streptococcus*, *Prevotella*, *Veillonella*, *Leptotrichia*, and *Actinobacillus* members with distinct microbial profiles associated with ESCC and EAC. In ESCC, *Streptococcus* species, *Veillonella parvula*, and *Porphyromonas gingivalis* are the most abundant species, whereas *Lautropia*, *Bulleidia*, *Catonella*, *Corynebacterium*, *Moryella*, *Peptococcus*, *Treponema*, and *Cardio bacterium* genera are depleted (Figure 1, Supplementary Table 1). Other studies have reported an increased abundance of Fusobacteria in ESCC compared with controls. In contrast, EAC patients show an enrichment of *Lactobacillus fermentum*, *Prevotella*, *Leptotrichia*, *Enterobacteriaceae*, and *Akkermansia muciniphila*, and a depletion of Streptococci, specifically *Streptococcus pneumoniae* (Figure 1, Supplementary Table 1).

Studies investigating cancer risk stratification based on microbial composition analysis have highlighted that *P. gingivalis*, *Streptococcus*, *Neisseria*, *Actinomyces*, and *Atopobium* are the main predictors for ESCC development, whereas lower ESCC risk is associated with the presence of *Prevotella* oral taxon 306 and *Aggregatibacter* paraphrophilus. Regarding EAC risk, an association with the periodontal pathogen *Tannerella forsythia* was identified, as well as other oral species including *Actinomyces cardiffensis*, *Selenomonas* oral taxon 134, and *Veillonella* oral taxon 917. Reduced EAC risk is linked to a higher abundance of Firmicutes (*Lachnocaraerobaculum umaense*, *Oribacterium parvum*, and *Solobacterium moorei*), Proteobacteria (*Neisseria sicca*, *Neisseria flavescens*, and *Haemophilus* oral taxon 908), *Corynebacterium durum*, *Prevotella nanceiensis*, and *S pneumoniae* (Figure 2). It remains to be determined whether these microbial changes have a causative effect or represent merely a consequence of the cancer being present.

**The Curious Case of Helicobacter pylori in EAC**

Epidemiologic evidence suggests an inverse relationship between *H pylori* eradication and EAC incidence, potentially induced by a shift in the gastric microbiota. A recent meta-analysis (72 studies including 84,717 cases and 390,749 controls) showed that *H pylori* infection was associated with a reduced risk for dysplastic BE. However, a large retrospective study of 36,803 US veterans could not confirm the association between either *H pylori* status or treatment status and EAC incidence. Similarly, a Swedish nationwide, population-based cohort study (*N* = 81,919) showed that *H pylori* status was associated inversely with BE, although a link with EAC incidence was not found. Furthermore, studies investigating the association between *H pylori* and reflux disease confirmed an increased risk of erosive reflux esophagitis after *H pylori* eradication, but did not show an increase in GERD-related symptoms. These contradictory findings highlight the need for a more comprehensive understanding of the role of *H pylori* in the development of esophageal cancer.

**Microbial Involvement in Esophageal Carcinogenesis: Mechanistic Insights**

Evidence from many preclinical models has shaped our mechanistic understanding of microbiota involvement in gastrointestinal carcinogenesis. Although the limitations of such models are extensive, it nevertheless remains that significant understanding and shaping of clinical studies has benefitted from these studies.

Through the use of nude mice xenograft studies, using intraperitoneal injection of esophageal cancer cells, significant alterations have occurred in the microbiota structure including a depletion of Pasteurellales and enrichment of carbohydrate/lipid metabolic pathways in the esophageal microbiota. Furthermore, fecal microbiota transplantation (FMT) of “healthy” mouse stool to antibiotic-treated xenograft-bearing mice significantly improved liver metastases, highlighting a protective role of the gut microbiota. Other xenograft models also have shown the effect of pathogenic species, including *P. gingivalis*, which induced epithelial mesenchymal transition within the esophagus and enhanced metabolic glucose uptake (Figure 3A).

Diet also has an impact on the microbiota composition in esophageal carcinogenesis. Sprague Dawley rats fed a high-fat diet (HFD) have an altered esophageal microbiota compared with rats fed a normal chow diet, with an increase in *Clostridium* species and depletion of *Escherichia*, *Shigella*, and *Lactobacillus* genera (Figure 3A). In addition, transgenic interleukin (IL)2–IL1β mice fed with a HFD developed esophageal tumors more rapidly than mice fed with a normal diet. This acceleration was associated with gut
microbiota changes as well as immune alterations including Toll-like receptor (TLR) expression, an increased ratio of neutrophils:natural killer cells, and aberrant levels of T-cell recruiting factors (chemokin [C-C motif] ligands 6 and 12: CCL6, CCL12), granulocyte colony-stimulating factor (G-CSF), and chemokine (C-X-C motif) ligand 1 (CXCL1), leading to an increase of C-X-C motif chemokine receptor 2 (CXCR2)-positive immune cells (Figure 3A). Organoid studies further confirmed that CXCR2 stimulation initiated expansion of Lgr5 progenitor cells, causing initiation of metaplasia.14

The proinflammatory effect of a HFD on the esophageal tract can be synergized further by the addition of deoxycholic acid to drinking water. Deoxycholic acid promotes the development of BE and chronic HFD + deoxycholic acid treatment results in a higher microbial diversity, an increase in inflammation, and a lipid tissue signature useful for early BE diagnosis.15

Figure 1. Overview on microbiota and cancers of the luminal GI tract. Bacterial genera/species abundantly present (blue arrow) or depleted (red arrow) in esophageal, gastric, and colorectal cancers.

Figure 2. Impact of the microbiota on GI cancers. The GI microbiota and its potential implications in cancer development, diagnostics, treatment interventions, and prevention by probiotics. CTLA-4, cytotoxic T-lymphocyte–associated protein 4; PD-L1, programmed cell death 1 ligand.
Surgical alteration of the upper gastrointestinal (GI) tract leads to functional modification affecting host metabolism and mucosal homeostasis. Esophagejejunostomy to induce BE in rats affects both TLR expression and esophageal microbiota composition, characterized by a significant decrease of *Lactobacillus* abundance and an increase of *Clostridium*, *Escherichia*, and *Shigella* depletion and acceleration in esophageal tumor development. The oral *P. gingivalis* pathogen alters the esophageal mucosal environment, resulting in epithelial mesenchymal transition induction and enhanced metabolic glucose uptake. Gastric colonization of INS-GAS (insulin-gastrin) mice with an intestinal flora (including *Clostridium*, *Lactobacillus*, and *Bacteroides* species) in combination with *H. pylori* infection induced a strong inflammation as characterized by an increased expression of IL11 and the cancer-related genes *Ptger4* and *Tgf-β* and the development of spasmyotic polypeptide-expressing metaplasia (SPEM), possibly mediated by the yes-associated protein 1 (YAP1) in GC, a HFD induces gastric dysbiosis (characterized by increased *Lactobacillus* abundance), intestinal metaplasia, the expression of leptin, phosphorylated leptin receptor and STAT3 and intracellular β-catenin accumulation. In the context of CRC, certain microbes such as *E. coli*, *P. anaerobius*, and *B. fragilis* are able to produce toxins that can influence carcinogenic processes. These include the induction of the DNA damage checkpoint pathway and proinflammatory responses, TLR interaction, impairment of the antitumor T-cell response, nuclear factor-κB (NF-κB), and Wnt/β-catenin pathway activation, further promoting cell proliferation. CCL, chemokin (C-C motif) ligand; c-MYC, MYC proto-oncogene; CXCR2, C-X-C motif chemokine receptor 2; EMT, epithelial-mesenchymal transition; G-CSF, granulocyte colony-stimulating factor; Hp, *H. pylori*; MUC4, mucin 4; PCWBR2, putative cell wall binding repeat 2; rASF, restricted altered Schaedler’s flora; ROS, reactive oxygen species; STAT3, signal transducer and activator of transcription 3.

**Gastric Cancer**

Gastric cancer (GC) is a multifactorial disease with different genetic, molecular, and environmental factors influencing disease development, with the most frequent...
cause being *H pylori* infection. This class I carcinogen plays a crucial role in initiating steps of gastric carcinogenesis by causing enhanced inflammation and progressive changes in the architecture and function of the gastric mucosa, resulting in a life-long infection unless an eradication strategy is implemented.55,56

Because of the acidic environment and other local antimicrobial factors, it was long thought that the stomach was inhabited exclusively by *H pylori* and was considered inhospitable to other microorganisms.57,58 However, from a certain timepoint in the course of progression of mucosal changes, gastric carcinogenesis is *H pylori*-independent because colonization levels decrease in patients with intestinal metaplasia and dysplasia, and essentially is absent by the adenocarcinoma stage. H pylori thus may act by a hit-and-run mechanism, priming the gastric mucosa for further oncogenic changes, which are accomplished by other microbes.55,57–60 Furthermore, stomach microhabitats are not always as uniform as previously thought. Local pH, mucin distribution, nutrients, ions, and chemical levels vary considerably in tumor and adjacent tumor-free tissue. These factors heavily influence microbial composition and diversity.57

Recent advances in sequencing technologies have highlighted significant differences in the gastric microbiota compared with the oral and/or esophageal microbiota, with the stomach harboring a distinct microbial ecosystem comprising Proteobacteria, Firmicutes, Bacteroidetes, Actinobacteria, and Fusobacteria.51,62 Studies also have shown the presence of a specific fungal consortium (mycobiome).63 One question that remains unanswered is related to transient vs persistent gastric colonization and its role in disease pathogenesis. Studies have tried to address this question, but the full potential of the gastric microbiota remains to be elucidated, including the contribution of the various gastric microbiota components and the extent of microbe:microbe crosstalk/interactions.64

**Microbiota Diversity in Gastric Carcinogenesis**

Studies assessing human gastric microbiota profiles have shown significant differences between patients with chronic (atrophic) gastritis, metaplasia, and GC, highlighting that dysbiosis in the stomach is a dynamic process that correlates with cancer progression (Supplementary Table 2).52,57,59,61,63–72 Microbiota profiles in patients with *H pylori*-induced superficial gastritis or even glandular atrophy are dominated by *Helicobacter* and, to a much lesser extent, *Streptococcus, Prevotella*, and *Neisseria*, resulting in decreased phytype richness, diversity, and evenness compared with patients with a normal gastric mucosa (Supplementary Table 2).73–78 The loss of specialized glandular tissue and decreased acid secretion in GC tissue results in *H pylori* loss and enrichment of intestinal commensals, including *Lactobacillus*, *Enterococcus*, *Carnobacterium*, *Parvimonas*, *Citrobacter*, *Clostridium*, *Achromobacter*, and *Rhodococcus*,55,67,79 as well as oral species; *Fusobacterium nucleatum*, *Veillonella*, *Leptotrichia*, *Haemophilus*, and *Campylobacter* (Figure 1, Supplementary Table 2).50,65,66,68–71,80 Furthermore, species, including *F nucleatum*, are associated with worse prognosis in Lauren’s diffuse-type GC (Supplementary Table 2).81 In addition to differences in microbial communities, metabolic pathways, including amino acid and nitrate metabolism, membrane transport, and carbohydrate digestion and absorption have been shown to be up-regulated in GC compared with healthy gastric tissue.55

Proton pump inhibitors (PPIs) frequently are used to treat GI disorders including erosive esophagitis and GERD. Although effective at improving GI symptoms, use of PPIs also promotes microbial growth that has genotoxic potential, with an increase in bacterial nitrate/nitrite reductase function, which is linked with cancer development.82 Moreover, the higher gastric pH, resulting from PPI use, can lead to an increase of *Peptostreptococcus stomatis*, *Streptococcus anginosus*, *Parvimonas micra*, *Stickia exigua*, and *Dialister pneumosintes*.83 It remains unclear whether microbiota changes resulting from PPI therapy influence an individual’s gastric cancer risk.

**Microbial Involvement in Gastric Carcinogenesis: Mechanistic Insights**

The differential susceptibility to *H pylori*-induced GC development has been partly attributed to differences in virulence of *H pylori* isolates, but also to the involvement of non-*H pylori* bacteria. Gastric colonization of INS-GAS mice (insulin-gastrin mice, with constitutional expression of gastrin regulated by the insulin promotor) with different types of intestinal microbes, including restricted altered Schaedler’s flora (ie, *Clostridium, Lactobacillus*, and *Bacteroides* species) and specific pathogen-free (with undefined complex intestinal flora) in combination with or without *H pylori* co-infection, showed that mice exposed to intestinal flora + *H pylori* co-infection show the strongest inflammatory responses, with 40% developing gastric cancer. This phenomenon also was seen in approximately 25% of mice exposed to restricted altered Schaedler’s flora (ASF) + *H pylori* co-infection. Furthermore, *H pylori* colonization induced the expression of IL11 and cancer-related genes *Ptger4* and *Tgf-β* (Figure 3B).33 In terms of host changes, ASF + *H pylori* co-infection colonization resulted in gastric mucosal changes including the development of spasmodic polypeptide-expressing metaplasia accompanied by aberrant mucin 4 (MUC4) expression and the presence of Ulex europaeus lectin–positive foveolar hyperplasia.24 This further supports a role for *H pylori* in accelerating gastric cancer development with the yes-associated protein 1, a key effector of the Hippo pathway, also being implicated in the process (Figure 3B).35 HFD also has been shown induce gastric dysbiotic changes including increased *Lactobacillus* abundance, intestinal metaplasia, expression of leptin, phosphorylated leptin receptor, and signal transducer and activator or transcription 3 (STAT3) and intracellular β-catenin accumulation (Figure 3B).36,37 whereas loss of the leptin receptor attenuates the effect of HFD on dysbiosis and intestinal metaplasia.37
Colorectal Cancer

In comparison with GC, in which a single microbe plays the dominant role, defining carcinogenic culprits from within the colonic microbiota and defining their involvement in colorectal cancer (CRC) development is incredibly challenging. Alterations in gut microbiota signatures consistently are reported in CRC, with tumor signatures differing from adjacent normal tissue. Differences include reduced diversity and altered community structure, which increase as CRC progresses (Supplementary Table 3).

Lower numbers of beneficial, potentially protective taxa, including butyrate-producing species belonging to Clostridium clusters IV and XIV, repeatedly are documented in CRC, whereas increased pro-oncogenic capacity has been attributed to an increase in species including Fusobacterium, Bacteroides, Campylobacter, Escherichia, and Porphyromonas (Figure 1, Supplementary Table 3). Firmicutes and Actinobacteria phyla and the Lachnospiraceae family are detected more frequently in premalignant adenomas, Proteobacteria, Alcaligenaceae, Enterobacteriaceae, and Sutterella species are increased in CRC (Figure 1, Supplementary Table 3). Studies also have suggested that specific species including Oscillospira are depleted in the transition from advanced adenoma to early CRC (Figure 1).

Key Players in Colorectal Carcinogenesis

F. nucleatum frequently is detected in CRC tissue, both at the adenoma and adenocarcinoma stages, in association with other oral commensal species, including Peptostreptococcus, Lactobacillus, and Campylobacter species (Figure 1, Supplementary Table 3). Its presence also is associated with an increased risk of CRC recurrence and development of chemoresistance. F. nucleatum impacts on CRC development in a number of ways: F. nucleatum frequently is detected at higher levels in the tumor microenvironment through its ability to localize with tumor-enriched lectins via the outer membrane protein (fatty acid binding protein 2, Fap2), and F. nucleatum modifies the tumor microenvironment; blocking natural killer cell antitumor responses and directing myeloid cell recruitment. F. nucleatum also influences microbial metastatic dissemination as microbiota signatures associated with Fusobacterium-enriched but not Fusobacterium-negative cancers detected in distant metastases.

Other bacteria that have been implicated in CRC pathogenesis include enterotoxigenic Bacteroides fragilis (ETBF) and Escherichia coli (shown to promote colon tumorigenesis in colitis-associated cancer rather than sporadic CRC), Streptococcus galloylactis subspecies galloylactis, and Enterococcus faecalis. The presence of B fragilis/ETBF in CRC tissue also is associated with a poorer prognostic outcome.

Although studies consistently indicate an increased abundance of Enterobacteriaceae (particularly E. coli) in inflamed colonic mucosa compared with uninflamed tissue, the evidence for E. coli involvement in CRC is associated predominantly with data from preclinical studies. Higher numbers of E. coli strains with the pks gene, which mediates production of the genotoxic colibactin, also have been found in the following: (1) CRC patients compared with controls, (2) CRC tissue compared with adjacent normal mucosa, and (3) late-stage compared with early stage CRC.

Microbial Biofilms and CRC

Bacterial biofilms have long been recognized as contributors to chronic infections and diseases in human beings, however, their role in intestinal cancers received limited consideration until seminal work by the Sears laboratory showed that invasive polymicrobial biofilms are present in many right-sided colonic tumors but only in a small proportion of left-sided tumors; findings that subsequently have been validated in other cohorts. Biofilm-positive tissues (tumor and normal mucosa) show well-established features of carcinogenesis including loss of E-cadherin and increased IL6 expression. Elucidation of CRC tissue biofilm composition showed specific microbial scaffolds: polymicrobial, polymicrobial with Fusobacteria, and Proteobacterial predominant. Biofilms also have been detected in familial adenomatous polyposis patients. In contrast to the sporadic CRC biofilms, familial adenomatous polyposis-associated biofilms were composed predominantly of ETBF and pks + E. coli.

Microbial Involvement in Colorectal Carcinogenesis: Mechanistic Insights

In the context of CRC, intestinal microbes impact via various mechanisms, with certain microbes being able to produce toxins that can influence carcinogenic processes. E. coli strains belonging to group B2 harbor a genomic island pks which encodes for the polyketide genotoxin colibactin (Figure 3). Infection with pks+ E. coli can result in enterocyte DNA double-strand breaks and activation of DNA damage checkpoint pathways, cell-cycle arrest, and cell death. Colibactin-positive E. coli also can lead to impairment of antitumor T-cell responses including a decrease in CD3+ and CD8+ T cells and an increase in colonic inflammation in APCmin/+ mice (mice carrying a point mutation in the murine APC gene) (Figure 3C). Furthermore, colibactin can shape gut microbiota composition/function, highlighting how microbes can compete for gut niche utilization. Interestingly, the carcinogenic effects of colibactin-producing E. coli are reversed by tumor necrosis factor blockade. F. nucleatum and Peptostreptococcus anaerobius are 2 anaerobic pathogens linked to CRC development. Both organisms adhere to the colonic mucosa and accelerate tumor development in APCmin/+ mice through interaction between outer membrane protein Fap2 (F. nucleatum) and putative cell wall binding repeat 2 protein and integrin α2/β1 (P. anaerobius). These interactions lead to increased cell proliferation and nuclear factor-kB activation, triggering proinflammatory responses including increased proinflammatory cytokine production and expansion of myeloid-derived suppressor cells, tumor-associated macrophages, and granulocytic tumor-associated neutrophils (Figure 3C). Furthermore, both pathogens interact with...
TLR2 and TLR4 on colonic epithelial cells, resulting in an increase of reactive oxygen species levels, further promoting cholesterol synthesis and cell proliferation (Figure 3C).42,106 ETBF originally was proposed as a microbial initiator of CRC based on the mechanism of action of its virulence factor fragilysin, which is one of the most potent known proinflammatory enterotoxins.84,107 Fragilysin binds to colonic epithelial receptors activating nuclear factor-κB signaling pathways, inducing increased cell proliferation, proinflammatory cytokine production, and direct DNA damage (Figure 3C). Fragilysin also induces cleavage of E-cadherin, resulting in increased Wnt/β-catenin (Wnt: wingless/integrated) signaling, an increase in cell proliferation, and expression of the protooncogene c-MYC (Figure 3C).43,108 A strong correlation between S. galloyticus and CRC also has been reported. S. galloyticus has the ability to colonize the intestinal tract and to promote tumor development in an azoxymethane-induced mice model of CRC, underscoring its importance in the functional relevance of CRC.109 However, more studies are needed to unravel the mechanisms involved.

Mechanistic evaluation of colonic mucosal biofilms has been performed using microbial slurries from human biofilm-positive CRC mucosa, human biofilm-positive non-CRC mucosa, and biofilm-negative mucosa, inoculated into CRC-susceptible mice.110 Biofilm-positive slurries induced robust invasive biofilm development, a phenomenon not seen in biofilm-negative slurries. Recruitment of immunosuppressive myeloid cells and associated IL17 production was seen within 1 week of biofilm-positive slurry inoculation, clearly showing the capacity of intestinal biofilms to drive intestinal mucosal changes and microbial architecture toward carcinogenesis. Further studies are needed to investigate biofilm-associated procarcinogenic and proinflammatory microbes as well as assessing their role in other gastrointestinal cancers.

Impact of the Microbiota on Diagnostic Tests

With altered microbiota signatures now being well accepted as a hallmark of progression in a number of gastrointestinal cancers, there is an ever-increasing interest in leveraging microbiota biomarker detection in cancer surveillance. Several studies have shown the value of including microbiota biomarker detection to complement existing screening tests and to improve early detection in CRC surveillance, with most success shown in the context of F. nucleatum (Figure 2).111–114 Inclusion of F. nucleatum detection, in combination with the fecal immunochemical test (FIT), improved the sensitivity for CRC (92.3% vs 73.1%) and for advanced adenoma (38.6% vs 15.5%) compared with FIT alone, supporting F. nucleatum as a valuable CRC marker that easily could be implemented in current practice (Figure 2).115 Furthermore, combining tests for F. nucleatum, P. stomatis, and several other species associated with CRC allowed an accurate classification of CRC patients with an area under the curve (AUC) of 0.84 and an odds ratio (OR) of 23 (Figure 2).114 Other studies have shown that the presence of P. micra, S. anginosus, and Proteobacteria in CRC resulted in an area under the concentration-time curve of 0.76, which increased to 0.83 when clinical markers were included (Figure 2).116 Efforts have been made to implement machine-learning models in predicting CRC based on the composition of the gut microbiota from stool samples.114,117–121 F. nucleatum, E. faecalis, Streptococcus bovis, B. fragilis, Porphyromonas species, Citrobacter species, and Slakia were identified as potential biomarkers for the diagnosis of CRC and adenomatous polyps (Figure 2).117–119,122–124 The combination of these bacterial candidates improved the diagnostic performance rather than assessment of each bacterium alone.124 In addition, microbe-derived metabolic signatures in stool or serum also have been considered as potential tools in CRC detection.125,126

There are less data on similar approaches for gastric or esophageal cancer. Profiling of microbiota coating the tongue has been assessed alongside serologic markers for early detection of GC.127 A predictive model also was developed that includes serologic testing of IgG anti–H. pylori antibody and pepsinogen, nitrosating/nitrate-reducing bacteria abundance, and type IV secretion system gene-contributing bacteria in the stomach.128 Both approaches have clear limitations and currently remain within the development space.

Impact on Cancer Treatment

Recently, there has been increasing interest in defining the impact of the gut microbiota on cancer treatment. There is a bidirectional interaction because many drugs are metabolized by gut bacteria, resulting in interindividual differences in drug metabolism and, thus, huge implications for efficacy and side effects of drugs across multiple disease indications.129 On the other hand, systemic treatments also have an effect on the composition and functioning of the microbiota.130

Chemotherapy

Platinum-based cytotoxic compounds mediate their effects through causing DNA damage, including formation of DNA adducts and intrastrand cross-links, which induces apoptosis. Although the majority of the current evidence is still from preclinical models, there is increasing understanding that the gastrointestinal microbiota might serve as predictive indicators for treatment response. Commensal bacteria can influence therapeutic effects of oxaliplatin by modulating the production of reactive oxygen species in tumor-infiltrating myeloid cells, which can enhance tumor regression.131 In the presence of antibiotics, oxaliplatin and cisplatin treatment reduce this effect and result in poorer survival in various murine models, with mice lacking TLR pathway components not able to respond to oxaliplatin. Cyclophosphamide, an alkylating anticancer agent, induces a reduction in regulatory T cells and increases the number of T helper (Th1) and Th17 cells as well as intestinal permeability.132,133 Viaud et al134 reported a specific association between luminal microbial
components and mucosal Th responses induced by cyclophosphamide treatment. Tumor-bearing mice with a reduced gut microbiota showed a reduction in Th17 cell numbers, with their tumors being refractory to cyclophosphamide treatment. Specifically, gram-positive bacteria Enterococcus hirae, Lactobacillus johnsonii, and Lactobacillus murinus, were shown to regulate cyclophosphamide efficacy (Figure 2); adoptive transfer of Th17 cells partially restored therapeutic efficacy. In the context of irinotecan treatment, targeted inhibition of gut bacterial β-glucuronidase enzymes improved cancer chemotherapeutic outcomes through a reduction in GI epithelial cell toxicity in preclinical models.

Other common CRC chemotherapeutic agents, including 5-fluorouracil, have been shown to induce gut dysbiosis in multiple preclinical studies, but do not seem to be affected by the gut microbiota in terms of their efficacy. After 5-fluorouracil and irinotecan therapy, levels of Enterobacteriaceae increase, whereas treatment with 5-fluorouracil alone also resulted in an increase of Staphylococcus and Clostridium species and a decrease of Bacteroides and Lactobacillus abundance.135,136

Radiotherapy

Radiation therapy is a core modality in cancer treatment and is associated with side effects including mucositis, dermatitis, and also bone marrow suppression.137 From both clinical and mechanistic studies, it is well documented that radiotherapy results in significant alteration of both gut microbiota abundance and diversity. Radiation treatment is associated with a reduction in Firmicutes and Bacteroidetes (although increases in Bacteroidetes also have been documented)138 along with a consistent increase in Proteobacteria, most often Enterobacteriaceae.139 Gerasszy-Vainberg et al138 showed that radiation treatment induced localized dysbiosis, which was associated with postradiation tissue damage. No studies have been published that assess the effect of the gut microbiota on the efficacy and outcome of radiotherapy, but there are data indicating that the gut microbiota impacts tissue radiosensitivity.140-142

Radiotherapy-induced diarrhea (RID) is a significant problem. Across the developed world, it is estimated that 150,000 to 300,000 patients require treatment for RID every year.143 The potential for ameliorating RID through probiotic supplementation has been a focus of recent studies.144 In an analysis of 8 trials with a total of 1116 participants, probiotics were associated with a lower risk of RID (relative risk, 0.62; 95% CI, 0.46-0.83) compared with placebo, but the baseline characteristics of the patients included were diverse. This notion also has been supported by a systematic review showing the potential of probiotics containing Lactobacillus species for the prevention of RID (Figure 2). However, additional well-designed research in the field is required.145

Immunotherapy

Multiple studies have highlighted the role of the gut microbiota in modulating immunotherapy efficacy across various cancers.146-149 Initial studies focused on understanding how the gut microbiota impacted CpG-oligonucleotide immunotherapy responses, which activates innate immune cells through TLR9.131 Subsequently, investigations assessed gut microbiota influence on immune-stimulatory cyclophosphamide chemotherapy treatment through shaping T-helper cell portfolios, namely the generation-specific subsets of Th17 and memory Th1 cells. More recently, the role of specific microbes was assessed in response to immune checkpoint inhibitor (ICI) therapies, including cytotoxic T-lymphocyte–associated protein 4 and programmed cell death 1 (PD-1)/PD-1 ligand inhibitors. Vétizou et al150 showed that the efficacy of anti-cytotoxic T-lymphocyte–associated protein 4 therapy was dependent on B fragilis and/or Bacteroides thetaiotaomicron and Burkholderiales populations, with T-cell responses specific for B fragilis and B thetaiotaomicron associated with therapeutic efficacy. In addition, the re-introduction of B fragilis cells and/or polysaccharides or adoptive transfer of B fragilis–specific T cells restored therapeutic efficacy and reduced immune-mediated colitis through activation of Th1 cells with cross-reactivity to bacterial antigens and tumor neoantigens (Figure 2).150,151 In terms of PD-1/PD-1 ligand acting agents, differences in clinical response have been linked to gut microbiota composition. In particular, an abundance of A muciniphila and E hirae have been shown to be more abundant in anti-PD-1 treatment responders compared with non-responders (Figure 2).147 This responder/nonresponder phenotype also has been shown to be transmissible because mice receiving FMT subsequently acquire donor responder/nonresponder efficacy. The nonresponsive phenotype was rescued by addition of A muciniphila alone or in combination with E hirae.

Taking the concept of the impact of the gut microbiota on ICI efficacy one step further, several studies investigated if FMT could safely and effectively improve response to ICI treatment in anti-PD-1-refractory patients.148,152,153 Anti-PD-1–refractory patients were given oral antibiotics (vancomycin and neomycin) and bowel preparation to deplete their microbiota, followed by FMT from donors who had achieved a complete response with anti–PD-1 therapy. Microbiota analysis confirmed that recipient gut microbiota

| Table 1. Unresolved Questions |
|-----------------------------|

| Question | Answer |
|----------|--------|
| What are the optimal methods for profiling microbiota changes in the context of disease progression as well as therapeutic regimens? | |
| What frequency of profiling is adequate to develop a comprehensive understanding of the microbiota? | |
| What other factors that influence the gut microbiota should be monitored alongside microbiota profiles? (For example age, diet, lifestyle, ethnicity, or concomitant medicines?) | |
| What is the ideal approach to microbial manipulation in the context of cancer therapies? | |
| What studies are needed to show cause-and-effect relationships between the gut microbiota and the pathogenesis of GI cancers? | |
profiles resembled donor profiles, although no microbial features clearly differentiated between responders and those who remained refractory. FMT treatment was shown to induce antitumor changes in immune cell infiltrates and gene expression profiles in the gut lamina propria and the tumor microenvironment.

**Impact of Probiotics on Postsurgical Outcome**

Digestive surgery has a dramatic effect on the microbiota, usually causing surgery-induced dysbiosis. Many factors may alter the overall microbial numbers/composition: bowel preparation, antibiotics, anesthesia, surgical stress, parenteral nutrition, and surgical anatomic changes. 

Loss of microbial diversity or abundance, an increase in potentially harmful species, and a decrease in beneficial species can slow wound healing and predispose patients undergoing abdominal surgery to infectious complications.

A recent systematic review (21 clinical trials with 1831 patients who were subjected to elective colorectal surgery) suggested that probiotics could significantly decrease inflammation, postoperative infectious complications, and the duration of antibiotic therapy. A similar conclusion was made by another meta-analysis, concluding that probiotics may have an effect on preventing postoperative infections and related complications in cancer patients undergoing surgery. A Chinese group studied the impact of a probiotic compound containing *Bifidobacterium infantis*, *Lactobacillus acidophilus*, *E faecalis*, and *Bacillus cereus* on serological inflammatory markers induced by gastrectomy. Probiotic supplementation significantly enhanced the immune response and reduced the severity of inflammation through modification of the gut microbiota (Figure 2). However, it remains unclear whether this results in an actual clinical benefit. Overall, there is a clear need for more evidence to draw conclusions about the efficacy of probiotics given before or after cancer surgery to provide evidence-based clinical recommendations.

**Summary and Glimpse to the Future**

We live in an increasingly microbiota-focused world, a world where we understand that microbes strongly shape health and disease, including cancer, although our appreciation is still in its infancy. With this knowledge comes the requirement to fully appreciate the mechanistic impact of the microbiota in cancer development as well as in therapeutic regimens including microbiota manipulation strategies. Please note, that supplementary tables 1-3 list a detailed overview of the current literature on the interaction of microbiota and esophageal, gastric and colorectal cancer. It is vital that we continue to increase our understanding because a number of unresolved questions remain (Table 1). Over the next few years, increasing emphasis on translating preclinical findings to the clinic setting is essential. As we move ever deeper into the precision medicine era, it has never been more important to be able to predict microbiota influence on human health.

**References**

1. Grice EA, Segre JA. The human microbiome: our second genome. Annu Rev Genomics Hum Genet 2012; 13:151–170.
2. Zhu B, Wang X, Li L. Human gut microbiome: the second genome of human body. Protein Cell 2010;1:718–725.
3. Sears CL, Garrett WS. Microbes, microbiota, and colon cancer. Cell Host Microbe 2014;15:317–328.
4. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Schistosomes, liver flukes and Helicobacter pylori. Lyon, June 7-14 1994. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans 1994;61:1–241.
5. Kostic AD, Chun E, Robertson L, Glickman JN, Gallini CA, Michaud M, Clancy TE, Chung DC, Lochhead P, Hold GL, El-Omar EM, Brenner D, Fuchs CS, Meyerson M, Garrett WS. Fusobacterium nucleatum potentiates intestinal tumorigenesis and modulates the tumor-immune microenvironment. Cell Host Microbe 2013;14:207–215.
6. Louis P, Hold GL, Flint HJ. The gut microbiota, bacterial metabolites and colorectal cancer. Nat Rev Microbiol 2014;12:661–672.
7. Arthur JC, Perez-Chanona E, Mühlbauer M, Tomkovich S, Uronis JM, Pan T-J, Campbell BJ, Abujameil T, Dogan B, Rogers AB, Rhodes JM, Stintzi A, Simpson KW, Hansen JJ, Keku TO, Fodor AA, Jobin C. Intestinal inflammation targets cancer-inducing activity of the microbiota. Science 2012;338:120–123.
8. Silva E, Teixeira A, David L, Carneiro F, Reis CA, Sobrino-Simões J, Serpa J, Veerman E, Bolscher J, Sobrino-Simões M. Mucins as key molecules for the classification of intestinal metaplasia of the stomach. Virchows Arch 2002;440:311–317.
9. Arnold M, Soerjomataram I, Ferlay J, Forman D. Global incidence of oesophageal cancer by histological subtype in 2012. Gut 2015;64:381–387.
10. Gregson EM, Bornschein J, Fitzgerald RC. Genetic progression of Barrett’s oesophagus to oesophageal adenocarcinoma. Br J Cancer 2016;115:403–410.
11. Li M, Shao D, Zhou J, Gu J, Qin J, Chen W, Wei W. Signatures within esophageal microbiota with progression of esophageal squamous cell carcinoma. Chin J Cancer Res 2020;32:755–767.
12. Liu A-Q, Vogtmann E, Shao D-T, Abnet CC, Dou H-Y, Qin Y, Su Z, Wei W-Q, Chen W. A comparison of biopsy and mucosal swab specimens for examining the microbiota of upper gastrointestinal carcinoma. Cancer Epidemiol Biomarkers Prev 2019;28:2030–2037.
13. Peter S, Pendergraft A, VanDerPol W, Wilcox CM, Kyanam Kabir Baig KR, Morrow C, Izard J, Mannon PJ. Mucosa-associated microbiota in Barrett’s esophagus, dysplasia, and esophageal adenocarcinoma differ similarly compared with healthy controls. Clin Transl Gastroenterol 2020;11:e00199.
14. Chen X, Winckler B, Lu M, Cheng H, Yuan Z, Yang Y, Jin L, Ye W. Oral microbiota and risk for esophageal squamous cell carcinoma in a high-risk area of China. PLoS One 2015;10:e0143603.
15. Liu Y, Lin Z, Lin Y, Chen Y, Peng X-E, He F, Liu S, Yan S, Huang L, Lu W, Xiang Z, Hu Z. Streptococcus and Prevotella are associated with the prognosis of oesophageal squamous cell carcinoma. J Med Microbiol 2018;67:1058–1068.

16. Li D, He R, Hou G, Ming W, Fan T, Chen L, Zhang L, Jiang W, Wang W, Lu Z, Feng H, Geng Q. Characterization of the esophageal microbiota and prediction of the metabolic pathways involved in esophageal cancer. Front Cell Infect Microbiol 2020;10:268.

17. Shao D, Vogtmann E, Liu A, Qin J, Chen W, Abnet CC, Wei W. Microbial characterization of esophageal squamous cell carcinoma and gastric cardia adenocarcinoma from a high-risk region of China. Cancer Prevention Research 2019;12:3993–4002.

18. Elliott DRF, Walker AW, O’Donovan M, Parkhill J, Fitzgerald RC. A non-endoscopic device to sample the esophageal microbiota: a case-control study. Lancet Gastroenterol Hepatol 2017;2:32–42.

19. Lopetuso LR, Severgnini M, Pecere S, Ponziani FR, Boskoski I, Larghi A, Quaranta G, Masucci L, Ianigo G, Camboni T, Gasbarrini A, Costamagna G, Consolandi C, Cammarota G. Esophageal microbiome signature in patients with Barrett’s esophagus and esophageal adenocarcinoma. PLoS One 2020;15:e0231789.

20. Snider EJ, Compres G, Freedberg DE, Khiabanian H, Nobel YR, Stump S, Uhlemann A-C, Lightdale CJ, Abrams JA. Alterations to the esophageal microbiome following infection with Helicobacter pylori and specified intestinal microbiota in the Helicobacter pylori INS-GAS mouse model of gastric carcinogenesis. J Histochem Cytochem 2019;67:4575–573.

21. Wang Q, Tao Y, Guo X, Liu N, Liu S, Wen P, Li S, Li Y. Oral microbiome in patients with oesophageal squamous cell carcinoma. Sci Rep 2019;9:19055.

22. Peters BA, Wu J, Pei Z, Yang L, Purdue MP, Freedman ND, Jacobs EJ, Gapstur SM, Hayes RB, Ahn J. Oral microbiome composition reflects prospective risk for esophageal cancers. Cancer Res 2017;77:6777–6787.

23. Chow WH, Blaser MJ, Blot WJ, Gammon MD, Vaughan TL, Risch HA, Perez-Perez GI, Schoenberg JB, Stanford JL, Rotterdam H, West AB, Fraumeni JFJ. An inverse relation between cagA+ strains of Helicobacter pylori infection and risk of esophageal and gastric cardia adenocarcinoma. Cancer Res 1998;58:588–590.

24. Nie S, Chen T, Yang X, Huai P, Lu M. Association of Helicobacter pylori infection with esophageal adenocarcinoma and squamous cell carcinoma: a meta-analysis. Dis Esophagus 2014;27:645–653.

25. Peek RMJ, Blaser MJ. Helicobacter pylori and gastrointestinal tract adenocarcinomas. Nat Rev Cancer 2002;2:28–37.

26. Eröss B, Farkas N, Vincze Á, Tinusz B, Szapáry L, Garam A, Balaskó M, Sarlós P, Czopf L, Alizadeh H, Rakonczay ZJ, Habon T, Hegyi P. Helicobacter pylori infection reduces the risk of Barrett’s esophagus: a meta-analysis and systematic review. Helicobacter 2018;23:e12504.

27. Kumar S, Metz DC, Ginsberg GG, Kaplan DE, Goldberg DS. Oesophageal and proximal gastric adenocarcinomas are rare after detection of Helicobacter pylori infection. Aliment Pharmacol Ther 2020;51:781–788.

28. Doorakers E, Lagergren J, Santoni G, Engstrand L, Brusselslaers N. Helicobacter pylori eradication treatment and the risk of Barrett’s esophagus and esophageal adenocarcinoma. Helicobacter 2020;25:e12688.

29. Iijima K, Koike T, Shimosegawa T. Reflux esophagitis triggered after Helicobacter pylori eradication: a noteworthy demerit of eradication therapy among the Japanese? Front Microbiol 2015;6:566.

30. Cheung MK, Yue GGL, Tsui KY, Gomes AJ, Kwan HS, Chiu PWY, Lau CBS. Discovery of an interplay between the gut microbiota and esophageal squamous cell carcinoma in mice. Am J Cancer Res 2020;10:2409–2427.

31. Chen M-F, Lu M-S, Hsieh C-C, Chen W-C. Porphyromonas gingivalis promotes tumor progression in esophageal squamous cell carcinoma. Cell Oncol (Dordr) 2021;44:373–384.

32. Kaaakoush NO, Lecomte V, Maloney CA, Morris MJ. Cross-talk among metabolic parameters, esophageal microbiota, and host gene expression following chronic exposure to an obesogenic diet. Sci Rep 2017;7:45753.

33. Lertpiriyapong K, Whary MT, Muthupalani S, Lofgren JL, Gamaon EER, Feng Y, Ge Z, Wang TC, Fox JG. Gastric colonisation with a restricted commensal microbiota replicates the promotion of neoplastic lesions by diverse intestinal microbiota in the Helicobacter pylori INS-GAS mouse model of gastric carcinogenesis. Gut 2014;63:54–63.

34. Pinzon-Guzman C, Meyer AR, Wise R, Choi E, Muthupalani S, Wang TC, Fox JG, Goldenring JR. Evaluation of lineage changes in the gastric mucosa following infection with Helicobacter pylori and specified intestinal flora in INS-GAS mice. J Histochem Cytochem 2019;67:53–63.

35. Wu Y, Shen L, Liang X, Li S, Ma L, Zheng L, Li T, Yu H, Chan H, Chen C, Yu J, Jia J. Helicobacter pylori-induced YAP1 nuclear translocation promotes gastric carcinogenesis by enhancing IL-1β expression. Cancer Med 2019;8:3965–3980.

36. Arita S, Ogawa T, Murakami Y, Kinoshita Y, Okazaki M, Inagaki-Ohara K. Dietary fat-accelerating leptin signaling promotes protumorigenic gastric environment in mice. Nutrients 2019;11:2127.

37. Arita S, Inagaki-Ohara K. High-fat-diet-induced modulations of leptin signaling and gastric microbiota drive precancerous lesions in the stomach. Nutrition 2019;67–68:101556.

38. Nougayrède J-P, Homburg S, Boury M, Brzuszkiewicz E, Gottschalk G, Buchrieser C, Hacker J, Dobrindt U, Oswald E. Escherichia coli induces DNA double-strand breaks in eukaryotic cells. Science 2006;313:848–851.

39. Pieleguexuelos-Manzano C, Puschhof J, Rosendahl Huber A, van Hoeck A, Wood HM, Nomburg J, Guroso C, Manders F, Dalmasso G, Stege PB, Paganelli FL, Geurts MH, Beumer J, Mizutani T, Miao Y, van der Linden R, van der Elst S, Garcia KC, Top J, Willems RJL,
46. Kohata Y, Nakahara K, Tanigawa T, Yamagami H, Münch NS, Fang H-Y, Ingermann J, Maurer HC, Wu S, Rhee K-J, Zhang M, Franco A, Sears CL. Bacteroides fragilis toxin stimulates intestinal epithelial cell shedding and gamma-secretase-dependent E-cadherin cleavage. J Cell Sci 2007;120:1944–1952.

47. Zaidi AH, Kelly LA, Kreft RE, Barlek M, Omstead AN, Liu X, Shao L, Liu X, Ji F, Mei Y, Cheng Y, Liu F, Yan C, Li L, Ling Z. Alterations of gastric mucosal microbiota across different stomach microhabitats in a cohort of 276 patients with gastric cancer. EBioMedicine 2019;40:336–348.

48. Sawada A, Fujiwara Y, Nagami Y, Tanaka F, Yamagami H, Tanigawa T, Shiba M, Tominaga K, Watanabe T, Gi M, Waniubuchi H, Arakawa T. Alteration of esophageal microbiome by antibiotic treatment does not affect incidence of rat esophageal adenocarcinoma. Dig Dis Sci 2016;61:3161–3168.

49. Pan F, Xu X, Zhang L-L, Luo H-J, Chen Y, Long L, Wang X, Zhuang P-T, Li E-M, Xu L-Y. Dietary riboflavin deficiency induces genomic instability of esophageal squamous cells that is associated with gut microbiota dysbiosis in rats. Food Funct 2020;11:10070–10083.

50. Pan F, Zhang L-L, Luo H-J, Chen Y, Long L, Wang X, Zhuang P-T, Li E-M, Xu L-Y. Dietary riboflavin deficiency induces arboflavinosis and esophageal epithelial atrophy in association with modification of gut microbiota in rats. Eur J Nutr 2021;60:807–820.

51. Jużenas S, Saltenienė V, Kupcinskas J, Link A, Kiudelis G, Jonaitis L, Jarmalaite S, Kupcinskas L, Malfertheiner P, Skiecieviene J. Analysis of deregulated microRNAs and their target genes in gastric cancer. PLoS One 2015;10:e0132327.

52. Kupcinskas J, Wex T, Link A, Bartuseviucite R, Dedelaite M, Kevalaitė G, Leja M, Skiecieviene J, Kiudelis G, Jonaitis L, Kupcinskas L, Malfertheiner P. PSCA and MUC1 gene polymorphisms are associated with gastric cancer and pre-malignant gastric conditions [corrected]. Anticancer Res 2014;34:7167–7175.

53. Kupcinskas L, Wex T, Kupcinskas J, Leja M, Ivanauskas A, Jonaitis LV, Janciauskas D, Kiudelis G, Funka K, Sudrab A, Chiu H-M, Lin J-T, Malfertheiner P. Interleukin-1B and interleukin-1 receptor antagonist gene polymorphisms are not associated with premalignant gastric conditions: a combined haplotype analysis. Eur J Gastroenterol Hepatol 2010;22:1189–1195.

54. Petkevicius V, Salteniene V, Juženas S, Wex T, Link A, Leja M, Steponaitiene R, Skiecieviene J, Kupcinskas L, Jonaitis L, Kiudelis G, Malfertheiner P, Kupcinskas J. Polymorphisms of microRNA target genes IL12B, INSR, CCND1 and IL10 in gastric cancer. World J Gastroenterol 2017;23:3480–3487.

55. Ferreira RM, Pereira-Marques J, Pinto-Ribeiro I, Costa JL, Caramelo F, Machado JC, Figueiredo C. Gastric microbial community profiling reveals a dysbiotic cancer-associated microbiota. Gut 2018;67:226–236.

56. Amieva M, Peek RMJ. Pathobiology of Helicobacter pylori-induced gastric cancer. Gastroenterology 2016;150:64–78.

57. Liu X, Shao L, Liu X, Ji F, Mei Y, Cheng Y, Liu F, Yan C, Li L, Ling Z. Alterations of gastric mucosal microbiota across different stomach microhabitats in a cohort of 276 patients with gastric cancer. EBioMedicine 2019;40:336–348.

58. Kupcinskas J, Hold GL. Other Helicobacters and the gastric microbiome. Helicobacter 2018;23(Suppl 1): e12521.

59. Hu Y-L, Pang W, Huang Y, Zhang Y, Zhang C-J. The gastric microbiome is perturbed in advanced gastric adenocarcinoma identified through shotgun metagenomics. Front Cell Infect Microbiol 2018;8:433.

60. Rajilic-Stojanovic M, Figueiredo C, Smet A, Hansen R, Kupcinskas J, Rokkas T, Andersen L, Machado JC, Janiro G, Gasbarrini A, Leja M, Gisbert JP, Hold GL. Systematic review: gastric microbiota in health and disease. Aliment Pharmacol Ther 2020;51:582–602.

61. Aviles-Jimenez F, Vazquez-Jimenez F, Medrano-Guzman R, Mantilla A, Torres J. Stomach microbiota composition varies between patients with non-atrophic deficiency.
62. Engstrand L, Lindberg M. Helicobacter pylori and the gastric microbiota. Best Pract Res Clin Gastroenterol 2013;27:39–45.

63. Hansen ABR, Johannesen TB, Spiegelhauer MR, et al. Distinct composition and distribution of the gastric mycobiota observed between dyspeptic and gastric cancer patients evaluated from gastric biopsies. Microb Heal Dis 2020;2:e340.

64. Spiegelhauer MR, Kucipinskas J, Johannesen TB, Urba M, Skieceviciene J, Jonaitis L, Frandsen TH, Kucipinskas L, Fuersted K, Andersen LP. Transient and persistent gastric microbiome: adherence of bacteria in gastric cancer and dyspeptic patient biopsies after washing. J Clin Med 2020;9:1882.

65. Yu G, Torres J, Hu N, Medrano-Guzman R, Herrera-Goepfert R, Humphries MS, Wang L, Wang C, Ding T, Ravel J, Taylor PR, Abnet CC, Goldstein AM. Molecular characterization of the human stomach microbiota in gastric cancer patients. Front Cell Infect Microbiol 2017;7:302.

66. Yang I, Woltemate S, Piazuelo MB, Bravo LE, Yepez MC, Romero-Gallo J, Delgado AG, Wilson KT, Peek RM, Correa P, Josenhans C, Fox JG, Suerbaum S. Different gastric microbiota compositions in two human populations with high and low gastric cancer risk in Colombia. Sci Rep 2016;6:18594.

67. Hsieh Y-Y, Tung S-Y, Pan H-Y, Yen C-W, Xu H-W, Lin Y-J, Deng Y-F, Hsu W-T, Wu C-S, Li C. Increased abundance of Clostridium and Fusobacterium in gastric microbiota of patients with gastric cancer in Taiwan. Sci Rep 2018;8:158.

68. Gao J-J, Zhang Y, Gerhard M, Mejias-Luque R, Zhang L, Vieth M, Ma J-L, Bajbouj M, Suchaneck S, Liu W-D, Ullm K, Quante M, Li Z-X, Zhou T, Schmid R, Classen M, Li W-Q, You W-C, Pan K-F. Association between gut microbiota and Helicobacter pylori-related gastric lesions in a high-risk population of gastric cancer. Front Cell Infect Microbiol 2018;8:202.

69. Castaño-Rodríguez N, Goh K-L, Fock KM, Mitchell HM, Kaaalouss NO. Dysbiosis of the microbiome in gastric carcinogenesis. Sci Rep 2017;7:15957.

70. Coker OO, Dai Z, Nie Y, Zhao G, Cao L, Nakatsu G, Wu WK, Wong SH, Chen Z, Sung JYY, Yu J. Mucosal microbiome dysbiosis in gastric carcinogenesis. Gut 2018;67:1024–1032.

71. Dicksved J, Lindberg M, Rosenquist M, Enroth H, Jansson JK, Engstrand L. Molecular characterization of the stomach microbiota in patients with gastric cancer and in controls. J Med Microbiol 2009;58:509–516.

72. Eun CS, Kim BK, Han DS, Kim SY, Kim KM, Choi BY, Song KS, Kim YS, Kim JF. Differences in gastric mucosal microbiota profiling in patients with chronic gastritis, intestinal metaplasia, and gastric cancer using pyrosequencing methods. Helicobacter 2014;19:407–416.

73. Parsons BN, Ijaz UZ, D’Amore R, Burkitt MD, Eccles R, Lenzi L, Duckworth CA, Moore AR, Tiszlavicz L, Varro A, Hall N, Pritchard DM. Comparison of the human gastric microbiota in hypochlorhydric states arising as a result of Helicobacter pylori-induced atrophic gastritis, autoimmune atrophic gastritis and proton pump inhibitor use. PLoS Pathog 2017;13:e1006653.

74. Sohn S-H, Kim N, Jo HJ, Kim J, Park JH, Nam RH, Seok Y-J, Kim Y-R, Lee DH. Analysis of gastric body microbiota by pyrosequencing: possible role of bacteria other than Helicobacter pylori in the gastric carcinogenesis. J Cancer Prev 2017;22:115–125.

75. Thorell K, Bengtsson-Palme J, Liu OH-F, Palacios Gonzales RV, Nookaew I, Rabeneck L, Paszaz L, Graham DY, Nielsen J, Lundin SB, Å Sjöling. In vivo analysis of the viable microbiota and Helicobacter pylori transcriptome in gastric infection and early stages of carcinogenesis. Infect Immun 2017;85:e00031–17.

76. Vuik F, Dicksved J, Lam SY, Fuhler GM, van der Laan L, van de Winkel A, Konstantinov SR, Spaander M, Peppelenbosch MP, Engstrand L, Kuipers EJ. Composition of the mucosa-associated microbiota along the entire gastrointestinal tract of human individuals. United Eur Gastroenterol J 2019;7:897–907.

77. Miao R, Wan C, Wang Z. The relationship of gastric microbiota and Helicobacter pylori infection in pediatrics population. Helicobacter 2020;25:13–22.

78. Han HS, Lee S-Y, Oh SY, Moon HW, Cho H, Kim J-H. Correlations of the gastric and duodenal microbiota with histological, endoscopic, and symptomatic gastritis. J Clin Med 2019;8:312.

79. Gantuya B, El Serag HB, Matsumoto T, Ajami NJ, Uchida T, Oyuntsetseg K, Bolor D, Yamaoka Y. Gastric mucosal microbiota in a Mongolian population with gastric cancer and precursor conditions. Aliment Pharmacol Ther 2020;51:770–780.

80. Gantuya B, El-Serag HB, Matsumoto T, Ajami NJ, Oyuntsetseg K, Azzaya D, Uchida T, Yamaoka Y. Gastric microbiota in Helicobacter pylori-negative and -positive gastritis among high incidence of gastric cancer area. Cancers (Basel) 2019;11:504.

81. Boehm ET, Thon C, Kucipinskas J, Stepanoaitiene R, Skieceviciene J, Canbay A, Malferttheiner P, Link A. Fusobacterium nucleatum is associated with worse gastric carcinogenesis. J Med Microbiol 2019;68:583–589.

82. Amir I, Konikoff FM, Oppenheim M, Gophna U, Half EE. Dysbiosis of the stomach microbiota promotes colon tumorigenesis via activation of T helper type 17 T cell responses. Nat Med 2009;15:1016–1022.

83. Li Q, Yu H. The role of non-H. pylori bacteria in the development of gastric cancer. Am J Cancer Res 2020;10:2271–2281.

84. Wu S, Rhee K-J, Albesiano E, Rabizadeh S, Wu X, Yen H-R, Huso DL, Brancati FL, Wick E, McAllister F, Housseau F, Pardoll DM, Sears CL. A human colonic commensal promotes colon tumorigenesis via activation of T helper type 17 T cell responses. Nat Med 2009;15:1016–1022.

85. Nakatsu G, Li X, Zhou H, Sheng J, Wong SH, Wu WK, Ng SC, Tsai H, Dong Y, Zhang N, He Y, Kang Q, Cao L, Wang K, Zhang J, Liang Q, Yu J, Sung JYJ. Gut mucosal microbiome across stages of colorectal carcinogenesis. Nat Commun 2015;6:8727.
86. Feng Q, Liang S, Jia H, Stadmayar A, Tang L, Lan Z, Zhang D, Xia H, Xu X, Jie Z, Su L, Li X, Li J, Xiao L, Huber-Schönauer U, Niederseer D, Xu X, Al-Arna JD, Yang H, Wang J, Kristiansen K, Arumugam M, Tilg H, Datz C, Wang J. Gut microbiome development along the colorectal adenoma-carcinoma sequence. Nat Commun 2015;6:6528.

87. Drewes JL, White JR, Dejea CM, Fathi P, Iyadorai T, Vadivelu J, Roslani AC, Wick EC, Mongodin EF, Loke MF, Thulasi K, Gan HM, Goh KL, Chong HY, Kumar S, Wanyiri JW, Sears CL. High-resolution bacterial 16S rRNA gene profile meta-analysis and biofilm status reveal common colorectal cancer consortia. NPJ Biofilms Microbiomes 2017;3:34.

88. Scott AJ, Alexander JL, Merrifield CA, Cunningham D, Jobin C, Brown R, Alvery J, O’Keefe SJ, Gaskins HR, Teare J, Yu J, Hughes DJ, Verstraehen H, Burton J, O’Toole PW, Rosenberg DW, Marchesi JR, Kinross JM. International Cancer Microbiome Consortium consensus statement on the role of the human microbiome in carcinogenesis. Gut 2019;68:1624–1632.

89. Castellarin M, Warren RL, Freeman JD, Dreolini L, Krzywinski M, Strauss J, Barnes R, Watson P, Allen-Vercoe E, Moore RA, Holt RA. Fusobacterium nucleatum infection is prevalent in human colorectal carcinoma. Genome Res 2012;22:299–306.

90. Warren RL, Freeman DJ, Pleasance S, Watson P, Moore RA, Cochran K, Allen-Vercoe E, Holt RA. Co-occurrence of anaerobic bacteria in colorectal cancer. Clinic Infect Dis 2015;61(8):1632–1635.

91. Bullman S, Pedamallu CS, Sicinska E, Clark LE, Zhang X, Cai D, Neuberg D, Huang K, Guevara F, Elez E, Ogino S, Tabernero J, Fuchs CS, Hahn WC, Nuciforo P, Meyerson M. Analysis of Fusobacterium nucleatum colorectal adenocarcinoma enrichment by 16S rRNA sequencing. mSphere 2017;2(5).

92. Yang H, Wang J, Kristiansen K, Arumugam M, Tilg H, Huber-Schönauer U, Niederseer D, Xu X, Al-Aama JY, Zhang D, Xia H, Xu X, Jie Z, Su L, Li X, Li J, Xiao L, Huber-Schönauer U, Niederseer D, Xu X, Al-Arna JD, Yang H, Wang J, Kristiansen K, Arumugam M, Tilg H, Datz C, Wang J. Gut microbiome development along the colorectal adenoma-carcinoma sequence. Nat Commun 2015;6:6528.

93. Moore RA, Cochrane K, Allen-Vercoe E, Holt RA. Co-occurrence of anaerobic bacteria in colorectal carcinoma. Proc Natl Acad Sci U S A 2010;107:11537–11542.

94. Yu T, Guo F, Yu Y, Sun T, Ma D, Han J, Qian Y, Kryczek I, Sun D, Nagarsheth N, Chen Y, Chen H, Hong J, Zou W, Fang J-Y. Fusobacterium nucleatum promotes chemoresistance to colorectal cancer by modulating autophagy. Cell 2017;170:548–563.e16.

95. Abed J, Emgård JEM, Zamir G, Faroja M, Almogy G, Grenov A, Sol A, Naor R, Pikarsky E, Atlan KA, Mellul A, Chaushu S, Manson AL, Earl AM, Ou N, Brennan CA, Garrett WS, Bachrach G. Fap2 mediates Fusobacterium nucleatum colorectal adenocarcinoma enrichment by binding to tumor-expressed Gal-GalNAc. Cell Host Microbe 2016;20:215–225.

96. Purcell RV, Pearson J, Aitchison A, Dixon L, Frizelle FA, Keenan JL. Colonization with enterotoxigenic Bacteroides fragilis is associated with early-stage colorectal neoplasia. PLoS One 2017;12:e0171602.

97. Viljoen KS, Dakshinamurthy A, Goldberg P, Blackburn JM. Quantitative profiling of colorectal cancer-associated bacteria reveals associations between fusobacterium spp., enterotoxigenic Bacteroides fragilis (ETBF) and clinicopathological features of colorectal cancer. PLoS One 2015;10:e0119462.

98. Boleij A, Hechenbleikner EM, Goodwin AC, Badani R, Stein EM, Lazarev MG, Ellis B, Carroll KC, Albesiano E, Wick EC, Platz EA, Pardoll DM, Sears CL. The Bacteroides fragilis toxin gene is prevalent in the colon mucosa of colorectal cancer patients. Clin Infect Dis 2015;60:208–215.

99. Bonnet M, Buc E, Sauvanet P, Darcha C, Dubois D, Pereira B, Déchelotte P, Bonnet R, Pezet D, Darfeuille-Michaud A. Colonization of the human gut by E. coli and colorectal cancer risk. Clin Cancer Res 2014;20:859–867.

100. Dejea CM, Wick EC, Hechenbleikner EM, White JR, Mark Welch JL, Rossetti BJ, Peterson SN, Nesruden EC, Borisy GG, Lazarev M, Stein E, Vadivelu J, Roslani AC, Malik AA, Wanyiri JW, Goh KL, Thervambiga I, Fu K, Fan W, Liosa N, Housseau F, Romans K, Wu X, McAllister FM, Wu S, Vogelstein B, Kinzler KW, Pardoll DM, Sears CL. Microbiota organization is a distinct feature of proximal colorectal cancers. Proc Natl Acad Sci U S A 2014;111:18321–18326.

101. Dejea CM, Fathi P, Craig JM, Boleij A, Taddese R, Geis AL, Wu X, DeStefano Shields CE, Hechenbleikner EM, Huso DL, Anders RA, Giardiello FM, Wick EC, Wang H, Wu S, Pardoll DM, Housseau F, Sears CL. Patients with familial adenomatous polyposis harbor colonic biofilms containing tumorigenic bacteria. Science 2018;359:592–597.

102. Buc E, Dubois D, Sauvanet P, Raisch J, Delmas J, Darfeuille-Michaud A, Pezet D, Bonnet R. High prevalence of mucosa-associated E. coli producing cyclo-modulin and genotoxin in colon cancer. PLoS One 2013;8:e56964.

103. Cuevas-Ramos G, Petit CR, Marcq I, Boury M, Oswald E, Nougayrède J-P. Escherichia coli induces DNA damage in vivo and triggers genomic instability in mammalian cells. Proc Natl Acad Sci U S A 2010;107:11537–11542.

104. Tronnet S, Floc'h P, Lucarelli L, Gaillard D, Martin P, Serino M, Oswald E. The genotoxin colibactin shapes gut microbiota in mice. mSphere 2020;5:e00569–20.

105. Yang Y, Gharibeh RZ, Newsome RC, Jobin C. Amending microbiota by targeting intestinal inflammation with TNF blockade attenuates development of colorectal cancer. Nat Cancer 2020;1:723–734.

106. Park S-R, Kim D-J, Han S-H, Kang M-J, Lee J-Y, Jeong Y-J, Lee S-J, Kim T-H, Ahn S-G, Yoon J-H,
87. Sears CL. Enterotoxigenic Bacteroides fragilis: a rogue among symbiotes. Clin Microbiol Rev 2009;22:349–369, Table of Contents.

107. Kumar R, Herold JL, Taylor J, Xu J, Xu Y. Variations among Streptococcus galyloticus subsp. galyloticus strains in connection with colorectal cancer. Sci Rep 2018;8:1514.

110. Tomkovich S, Dejea CM, Winglee K, Drewes JL, Park J-H. Diverse Toll-like receptors mediate cytokine production by Fusobacterium nucleatum and Aggregatibacter actinomycetemcomitans in macrophages. Infect Immun 2014;82:1914–1920.

108. Goulas T, Arolas JL, Gomis-Ruth FX. Structure, function and latency regulation of a bacterial enterotoxin poten
tially derived from a mammalian adamalysin/ADAM xenolog. Proc Natl Acad Sci U S A 2011;108:1856–1861.

117. Ai D, Pan H, Han R, Li X, Liu G, Xia LC. Using decision tree aggregation with random Forest model to identify gut microbes associated with colorectal cancer. Genes (Basel) 2019;10:112.

118. Ai L, Tian H, Chen Z, Chen H, Xu J, Fang J-Y. Systematic evaluation of supervised classifiers for fecal microbiota-based prediction of colorectal cancer. Oncotarget 2017; 8:9546–9556.

119. Kharrat N, Assidi M, Abu-Elmagd M, Pushparaj PN, Akhaldy A, Arfaoui L, Naseer MI, El Omri A, Messaoudi S, Buhmeida A, Rebai A. Data mining analysis of human gut microbiota links Fusobacterium spp. with colorectal cancer onset. Bioinformation 2019; 15:372–379.

120. Thomas AM, Manghi P, Asnicar F, Pasolli E, Armanini F, Zolo M, Beggini F, Manara S, Karcher N, Pozzi C, Gandini S, Serrano D, Tarallo S, Francavilla A, Gallo G, Trompetto M, Ferrero G, Mizutani S, Shiroma H, Shiba S, Shibata T, Yachida S, Yamada T, Wirbel J, Schrotz-King P, Ulrich CM, Brenner H, Arumugam M, Bork P, Zeller G, Cordero F, Dias-Neto E, Setubal JC, Tett A, Pardini B, Rescigno M, Waldron L, Naccarati A, Segata N. Metagenomic analysis of colorectal cancer datasets identifies cross-cohort microbial diagnostic signatures and a link with choline degradation. Nat Med 2019;25:667–678.

121. Zackular JP, Rogers MAM, Ruffin MT 4th, Schloss PD. The human gut microbiome as a screening tool for colorectal cancer. Cancer Prev Res (Phila) 2014; 7:1112–1121.

122. Eklöf V, Lögfn-Burström A, Zingmark C, Edin S, Larsson P, Karling P, Alexeyev O, Rutégård J, Wikberg ML, Palmqvist R. Cancer-associated fecal microbial markers in colorectal cancer detection. Int J Cancer 2017;141:2528–2536.

123. Mangifesta M, Mancabelli L, Milani C, Gaiani F, de’Angelis N, de’Angelis GL, van Sinderen D, Ventura M, Turroni F. Mucosal microbiota of intestinal polyps reveals putative biomarkers of colorectal cancer. Sci Rep 2018;8:13974.

125. Yang Y, Misra BB, Liang L, Bi D, Weng W, Wu W, Cai S, Qin H, Goel A, Li X, Ma Y. Integrated microbiome and metabolome analysis reveals a novel interplay between commensal bacteria and metabolites in colorectal cancer. Theranostics 2019;9:4101–4114.

126. Tan B, Qiu Y, Zou X, Chen T, Xie G, Cheng Y, Dong T, Zhao L, Feng B, Hu X, Xu L, Zhao A, Zhang M, Cai G, Cai S, Zhou Z, Zheng M, Zhang Y, Jia W. Metabonomics identifies serum metabolite markers of colorectal cancer. J Proteome Res 2013;12:3000–3009.

127. Wu J, Xu S, Xiang C, Cao Q, Li Q, Huang J, Shi L, Zhang J, Zhan Z. Tongue coating microbiota community and risk effect on gastric cancer. J Cancer 2018; 9:4039–4048.

128. Choi S, Lee JG, Lee A-R, Eun CS, Han DS, Park CH. Helicobacter pylori antibody and pepsinogen testing for predicting gastric microbiome abundance. PLoS One 2019;14:e0225961.
Radiation induces proinflammatory dysbiosis: transmission of inflammatory susceptibility by host cytokine induction. Gut 2018;67:97–107.

139. Toucheffeu Y, Montassier E, Nieman K, Gastinne T, Potel G, Bruley des Varannes S, Le Vacon F, de La Cochetière MF. Systematic review: the role of the gut microbiota in chemotherapy- or radiation-induced gastrointestinal mucositis - current evidence and potential clinical applications. Aliment Pharmacol Ther 2014;40:409–421.

140. Crawford PA, Gordon JJ. Microbial regulation of intestinal radiosensitivity. Proc Natl Acad Sci U S A 2005;102:13254–13259.

141. Cui M, Xiao H, Luo D, Zhang X, Zhao S, Zheng Q, Li Y, Zhao Y, Dong J, Li H, Wang H, Fan S. Circadian rhythm shapes the gut microbiota affecting host radiosensitivity. Int J Mol Sci 2016;17:1786.

142. Paulos CM, Wrzesinski C, Kaiser A, Hinrichs CS, Chieppa M, Cassard L, Palmer DC, Boni A, Muranski P, Yu Z, Gattinoni L, Antony PA, Rosenberg SA, Restifo NP. Microbial translocation augments the function of adoptively transferred self/tumor-specific CD8⁺ T cells via TLR4 signaling. J Clin Invest 2007;117:2197–2204.

143. Andreyev J. Gastrointestinal complications of pelvic radiotherapy: are they of any importance? Gut 2005;54:1051–1054.

144. Devaraj NK, Suppiah S, Veettil SK, Ching SM, Lee KW, Menon RK, Soo MJ, Deuraseh I, Hoo FK, Sivarathnam D. The effects of probiotic supplementation on the incidence of diarrhea in cancer patients receiving radiation therapy: a systematic review with meta-analysis and trial sequential analysis of randomized controlled trials. Nutrients 2019;11:2886.

145. Bowen JM, Gibson RJ, Coller JK, Blijlevens N, Bossi P, Al-Dasooqi N, Bateman EH, Chiang K, de Mooij C, Mayo B, Stringer AM, Tissing W, Wardill HR, van Sebille YZA, Ranna V, Vaddi A, Keefe DM, Lalla RV, Cheng KKF, Elad S. Systematic review of agents for the management of cancer treatment-related gastrointestinal mucositis and clinical practice guidelines. Support Care Cancer 2019;27:4011–4022.

146. Frankel AE, Coughlin LA, Kim J, Froehlich TW, Xie Y, Frenkel EP, Koh AY. Metagenomic shotgun sequencing and unbiased metabolomic profiling identify specific human gut microbiota and metabolites associated with immune checkpoint therapy efficacy in melanoma patients. Neoplasia 2017;19:845–855.
Gopalakrishnan V, Spencer CN, Nezi L, Reuben A, Andrews MC, Karpinets TV, Prieto PA, Vicente D, Hoffman K, Wei SC, Cogdill AP, Zhao L, Hudgens CW, Hutchinson DS, Manzo T, Petaccia de Macedo M, Cotechini T, Kumar T, Chen WS, Reddy SM, Szczepaniak Sloane R, Galloway-Pena J, Jiang H, Chen PL, Shpall EJ, Rezvani K, Alousi AM, Chemaly RF, Shelburne S, Vence LM, Okhuysen PC, Jensen VB, Swennes AG, McClister F, Marcelo Riquelme Sanchez E, Zhang Y, Le Chatelier E, Zitvogel L, Pons N, Austin-Breneman JL, Haydu LE, Burton EM, Gardner JM, Simrans E, Hu J, Lazar AJ, Tsujikawa T, Diab A, Tawbi H, Glitza IC, Hwu WJ, Patel SP, Woodman SE, Amaria RN, Davies MA, Gershenwald JE, Hwu P, Lee JE, Zhang J, Cossens LM, Cooper ZA, Futreal PA, Daniel CR, Ajami NJ, Petrosino JF, Tetzlaff MT, Sharma P, Allison JP, Jenq RR, Cooper ZA, Futreal PA, Daniel CR, Ajami NJ, Petrosino JF, Tetzlaff MT, Sharma P, Allison JP, Jenq RR, Wargo JA. Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients. Science 2018;359:97–103.

Matson V, Fessler J, Bao R, Chongsuwat T, Zha Y, Alegre M-L, Luke JJ, Gajewski TF. The commensal microbiome is associated with anti-PD-1 efficacy in metastatic melanoma patients. Science 2018; 359:104–108.

Vétizou M, Pitt JM, Daillère R, Woodman SE, Armand R, Davies MA, Gershenwald JE, Hwu P, Lee JE, Zhang J, Cossens LM, Cooper ZA, Futreal PA, Daniel CR, Ajami NJ, Petrosino JF, Tetzlaff MT, Sharma P, Allison JP, Jenq RR, Wargo JA. Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients. Science 2018;359:97–103.

Cramer P, Bresalier RS. Gastrointestinal and hepatic complications of immune checkpoint inhibitors. Curr Gastroenterol Rep 2017;19:3.

Baruch EN, Youngster I, Ben-Betzalel G, Ortenberg R, Lahat A, Katz L, Adler K, Dick-Neuclea D, Raskin S, Bloch N, Rotin D, Anafi L, Avivi C, Melnichenko J, Steinberg-Silman Y, Mantani R, Harati H, Asher N, Shapira-Frommer R, Gepbron P, Woerther P-L, Chachaty E, Chaput N, Robert C, Mateus C, Kroemer G, Raoul D, Boneca IG, Carbonnel F, Chamaillard M, Zitvogel L. Anticancer immunity by disruption or causality? Aliment Pharmacol Ther 2013;37:1084–1092.

Cass S, Hamilton C, Miller A, Jupiter D, Khanipov K, Booth A, Pyles R, Krill T, Reep G, Okereke I. Novel ex vivo model to examine the mechanism and relationship of esophageal microbiota and disease. BioMedicines 2021;9:142.

Deng Y, Tang D, Hou P, Shen W, Li H, Wang T, Liu R. Dysbiosis of gut microbiota in patients with esophageal cancer. Microb Pathog 2021;150:104709.

Deshpande NP, Riordan SM, Castaño-Rodríguez N, Wilkins MR, Kaakoush NO. Signatures within the esophageal microbiome are associated with host genetics, age, and disease. Microbiome 2018;6:227.

Gall A, Fero J, McCoy C, Claywell BC, Sanchez CA, Blount PL, Li X, Vaughan TL, Matsen FA, Reid BJ, Salama NR. Bacterial composition of the human upper gastrointestinal tract microbiome is dynamic and associated with genomic instability in a Barrett’s esophagus cohort. PLoS One 2015;10:e0129055.

Gao S, Li S, Ma Z, Liang S, Shan T, Zhang M, Zhu X, Zhang P, Liu G, Zhou F, Yuan X, Jia R, Potempa J, Scott DA, Lamont RJ, Wang H, Feng X. Presence of Porphyromonas gingivalis in esophagus and its association with the clinicopathological characteristics and survival in patients with esophageal cancer. Infect Agent Cancer 2016;11:3.

Nakiryō M, Tanabe C, Yamada Y, Igaki H, Tachimori Y, Kato H, Muto M, Montesano R, Sakamoto H, Nakajima Y, Sasaki H. Frequent and preferential infection of Treponema denticola, Streptococcus mitis, and Streptococcus anginosus in esophageal cancers. Can J Cancer 2016;11:3.

Snider EJ, Comprés G, Freedberg DE, Giddins MJ, Khiabanian H, Lightdale CJ, Nobel YR, Toussaint NC, Uhlemann A-C, Abrams JA. Barrett’s esophagus is...
associated with a distinct oral microbiome. Clin Transl Gastroenterol 2018;9:135.

168. Yamamura K, Baba Y, Nakagawa S, Mima K, Miyake K, Nakamura K, Sawayama H, Kinoshita K, Ishimoto T, Iwatsuki M, Sakamoto Y, Yamashita Y, Yoshida N, Watanabe M, Baba H. Human microbiome Fusobacterium nucleatum in esophageal cancer tissue is associated with prognosis. Clin Cancer Res 2016; 22:5574–5581.

169. Ahn J, Sinha R, Pei Z, Dominiani C, Wu J, Shi J, Goedert JJ, Hayes RB, Yang L. Human gut microbiome and risk for colorectal cancer. J Natl Cancer Inst 2013; 105:1907–1911.

170. Allali I, Delgado S, Marron PI, Astudillo A, Yeh JJ, Ghazal H, Amzazi S, Keku T, Azcarate-Peril MA. Gut microbiome compositional and functional differences between tumor and non-tumor adjacent tissues from cohorts of the US and Spain. Gut Microbes 2015; 6:161–172.

171. Chang H, Mishra R, Cen C, Tang Y, Ma C, Wasti S, Wang Y, Ou Q, Chen K, Zhang J. Metagenomic analyses expand bacterial and functional profiling biomarkers for colorectal cancer in a Hainan cohort, China. Curr Microbiol 2021; 78:705–712.

172. Chen C, Niu M, Pan J, Du N, Liu S, Li H, He Q, Mao J, Duan Y, Du Y. Bacteroides, butyric acid and t10,c12-CLA changes in colorectal adenomatous polypl patients. Gut Pathog 2021;13:1.

173. Chen H-M, Yu Y-N, Wang J-L, Lin Y-W, Kong X, Yang C-Q, Yang L, Liu Z-J, Yuan Y-Z, Liu F, Wu J-X, Zhong L, Fang D-C, Zou W, Fang J-Y. Decreased dietary fiber intake and structural alteration of gut microbiota in patients with advanced colorectal adenoma. Am J Clin Nutr 2013;97:1044–1052.

174. Coker OO, Wu WK, Wong SH, Sung JY, Yu J. Altered gut archaea composition and interaction with bacteria are associated with colorectal cancer. Gastroenterology 2020;159:1459–1470.e6.

175. Coker OO, Nakatsu G, Dai RZ, Wu WK, Wong SH, Ng SC, Chan FKL, Sung JY, Yu J. Enteric fungal microbiota dysbiosis and ecological alterations in colorectal cancer. Gut 2019;68:654–662.

176. Cremonesi E, Governa V, Garzon JFG, Mele V, Amicarella F, Muraro MG, TRELLA E, Galati-Fournier V, Oertli D, Däster SR, Droeser RA, Weixler B, Bolli M, Rosso R, Nitsche U, Khanna N, Eglí A, Keck S, Slotta-Huspenina J, Terracciano LM, Zajac P, Spagnoli GC, Eppenberger-Castori S, Janssen K-P, Borsig L, Iezzi G. Gut microbiota modulate T cell trafficking into human colorectal cancer. Gut 2018;67:1984–1994.

177. Dai Z, Coker OO, Nakatsu G, Wu WK, Zhao L, Chen Z, Chan FKL, Kristiansen K, Sung JY, Wong SH, Yu J. Multi-cohort analysis of colorectal cancer metagenome identified altered bacteria across populations and universal bacterial markers. Microbiome 2018;6:70.

178. Debesa-Tur G, Pérez-Brocal V, Ruiz-Ruiz S, Castillejo A, Latorre A, Soto JL, Moya A. Metagenomic analysis of formalin-fixed paraffin-embedded tumor and normal mucosa reveals differences in the microbiome of colorectal cancer patients. Sci Rep 2021;11:391.
191. Mira-Pascual L, Cabrera-Rubio R, Ocon S, Costales P, Parra A, Suarez A, Moris F, Rodrigo L, Mira A, Collado MC. Microbial mucosal colonic shifts associated with the development of colorectal cancer reveal the presence of different bacterial and archaeal biomarkers. J Gastroenterol 2015;50:167–179.

192. Nakatsu G, Zhou H, Wu WKK, Wong SH, Coker OO, Dai Z, Li X, Szeto C-H, Sugimura N, Lam TY-T, Yu AC-S, Wang X, Chen Z, Wong MC-S, Ng SC, Chan MTV, Chan PKS, Chan FKL, Sung JJ-Y, Yu J. Alterations in enteric virome are associated with colorectal cancer and survival outcomes. Gastroenterology 2018;155:529–541.e5.

193. Niccolai E, Russo E, Baldi S, Ricci F, Nannini G, Pedone M, Stingo FC, Taddei A, Rimpessi MN, Bechi P, Mengoni A, Fani R, Bacci G, Fagorzi C, Chiellini C, Prisco D, Ramazzotti M, Amedei A. Significant and conflicting correlation of IL-9 with Prevotella and Bacteroides in human colorectal cancer. Front Immunol 2020;11:573158.

194. Ohigashi S, Sudo K, Kobayashi D, Takahashi O, Takahashi T, Asahara T, Nomoto K, Onodera H. Changes of the intestinal microbiota, short chain fatty acids, and fecal pH in patients with colorectal cancer. Dig Dis Sci 2013;58:1717–1726.

195. Osman MA, Neoh H-M, Ab Matalib N-S, Chin S-F, Mazlan L, Raja Ali RA, Zakaria AD, Ngui CS, Ang MY, Jamal R. Parvimonas micra, Peptostreptococcus stomatitis, Fusobacterium nucleatum and Akkermansia muciniphila as a four-bacteria biomarker panel of colorectal cancer. Sci Rep 2021;11:2925.

196. Serrano D, Pozi C, Guglietta S, Fosso B, Suppa M, Gnagnarella P, Corso F, Bellerba F, Macis D, Aristanco V, Manghi P, Segata N, Trovato C, Zampino MG, Marzano M, Bonanni B, Rescigno M, Gandini S. Microbiome as mediator of diet on colorectal cancer risk: the role of vitamin D, markers of inflammation and adipokines. Nutrients 2021;13:363.

197. Sobhani I, Bergsten E, Couffin S, Amiot A, Nebbad B, Barau C, de’Angelis N, Rabot S, Canou PY-Poitren F, M estivier D, Pédro T, Khazaie K, Sansonetti PJ. Colorectal cancer-associated microbiota contributes to oncogenic epigenetic signatures. Proc Natl Acad Sci U S A 2019;116:24285–24295.

198. Sobhani I, Tap J, Rouot-Thoraval F, Roperch JP, Letulle S, Langella P, Corthier G, Tran Van Nhieu J, Future JP. Microbial dysbiosis in colorectal cancer (CRC) patients. PLoS One 2011;6:e16393.

199. Wang Y, Zhang Y, Qian Y, Xie Y-H, Jiang S-S, Kang Z-R, Chen Y-X, Chen Z-F, Fang J-Y. Alterations in the oral and gut microbiome of colorectal cancer patients and association with host clinical factors. Int J Cancer 2021, Epub ahead of print.

200. Wang Y, Wan X, Wu X, Zhang C, Liu J, Hou S. Eubacterium rectale contributes to colorectal cancer initiation via promoting colitis. Gut Pathog 2021;13:2.