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CANCER (RA MURPHY, SECTION EDITOR)

Diet, Microbes, and Cancer Across the Tree of Life: a Systematic Review

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Abstract

Purpose of Review Cancers are a leading cause of death in humans and for many other species. Diet has often been associated with cancers, and the microbiome is an essential mediator between diet and cancers. Here, we review the work on cancer and the microbiome across species to search for broad patterns of susceptibility associated with different microbial species.

Recent Findings Some microbes, such as *Helicobacter* bacteria, papillomaviruses, and the carnivore-associated *Fusobacteria*, consistently induce tumorigenesis in humans and other species. Other microbes, such as the milk-associated *Lactobacillus*, consistently inhibit tumorigenesis in humans and other species.

Summary We systematically reviewed over a thousand published articles and identified links between diet, microbes, and cancers in several species of mammals, birds, and flies. Future work should examine a larger variety of host species to discover new model organisms for human preclinical trials, to better understand the observed variance in cancer prevalence across species, and to discover which microbes and diets are associated with cancers across species. Ultimately, this could help identify microbial and dietary interventions to diagnose, prevent, and treat cancers in humans as well as other animals.

Keywords Microbiome · Oncobiome · Nutrition · Comparative oncology · Tumour · Probiotic

Introduction

Cancer is one of the world's leading causes of death (https://ourworldindata.org/cancer) [1–3]. Although it is known that microbes and diet affect cancer incidence, there has been no systematic review of the work across different host species to identify microbes and dietary factors that consistently contribute to cancer. Here, we fill that gap by reviewing the effect of diet and microbes on different species of mammals, birds, and flies. We begin with a brief overview of what is known about the human microbiome, diet, and cancer. Then, we discuss this information in the broader context of cancers across vertebrates.

Healthy Microbiome vs. Oncobiome

The gut microbiome is the entire population of microbes inhabiting the gut [4, 5]. Out of the ~ 100 trillion bacteria, viruses, archaea, fungi, and protozoa in our body, one hundred billion to one trillion of these microbes per litre are present in the colon [6–11]. In healthy individuals, approximately 90% of our gut microbes belong to the phyla Bacteroidetes and Firmicutes [8, 12–14]. The remaining 10% are Actinobacteria, *Fusobacteria*, Proteobacteria, and Verrucomicrobia [12, 15, 16].

The oncobiome [17], a collection of carcinogenic microbes, is estimated to cause cancer in 2.2 million people every year (over 10% of the world's cancer cases) [18]. An underrepresentation of species within the *Escherichia*,

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Citrobacter, *Shigella*, *Flavobacterium*, *Acinetobacter*, and *Chryseobacterium* genera has been noted in tumour tissues of patients with colorectal cancer [19]. A low relative abundance of *Lachnospiraceae* species, *Bifidobacterium animalis*, and *Streptococcus thermophilus* [20, 21] and a relatively high abundance of *Bacteroides clarus*, *Roseburia intestinalis*, *Clostridium hathewayi* [22], *Fusobacterium nucleatum* [23–25], *Parvimonas micra*, and *Solobacterium moorei* serve as biomarkers of colorectal cancer [26]. Infection with *Helicobacter pylori* bacteria positive for the CagA protein is associated with an increased risk of developing colorectal adenocarcinoma [27]. Bacteremia from *Clostridium septicum* increases the risk of developing colorectal cancer [28]. Firmicutes and *Lactococcus* are more abundant in the gut microbiota of colorectal cancerous tissues versus neighbouring colorectal noncancerous tissues [29]. *Helicobacter hepaticus* promotes the development of toxin- and virus-induced hepatocellular carcinoma [30]. *Clostridium difficile* [31, 32], *Enterococcus faecalis*, *Bacteroides fragilis*, *Escherichia coli*, *Streptococcus bovis/gallolyticus* [33, 34], *Porphyromonas*, *Peptostreptococcus*, *Gemella*, *Mogibacterium*, *Klebsiella* [35], and *Prevotella* [36] are relatively more abundant in patients with colorectal cancer than healthy individuals.

The fact that some microbes within the *Bacteroides* [22, 33, 34, 37] and *Bifidobacterium* taxa [20, 21] can both protect from and increase the risk of colorectal cancer in humans highlights the complexity, dynamics, intraindividual, and interindividual variation of the oncobiome.

Gut microbes are also associated with other types of cancer, such as hepatocellular carcinoma, prostate cancer, breast cancer, gastric adenocarcinoma, lymphoma, and cervical cancers. The intestinal bacteria *Helicobacter hepaticus* drive hepatocellular carcinoma, prostate cancer, and breast tumours [30]. *Helicobacter pylori,* hepatitis B virus, and human papillomaviruses drive gastric, hepatic, and cervical cancers [38]. *Helicobacter pylori* is also associated with lymphoma, prostate cancer, sarcoma, and pancreatic cancer, via several mechanisms including the regulation of inflammatory and endocrine pathways [39].

Diet-Associated Microbes and Their Effects on Cancer

The interaction of gut microbes with their hosts depends on many aspects of the external and internal environment. Dietary intake [40–43], drug exposures [43–46], host genetics [47–50], age [51], sex [52], lifestyle [53, 54], group living arrangements [55–57], and contact with soil [58–60] influence the gut microbiome. Diet is a key modulator of the gut microbiome and host tissue [41, 43, 54, 60–63], affecting the development of diseases such as cancer [64–66].

Specific diets have been linked with cancer in humans [64–67]. The consumption of diets rich in fibre, fruits, yoghurts, whole grains, extra virgin olive oil, vegetables, and low in animal products has been associated with lower rates of cancer [68–73]. On the other hand, highly processed food [74, 75], animal fats, red meat, and low intakes of dietary fibre are associated with higher cancer risk [76, 77]. Western diet-related microbial dysbiosis [78] also is associated with colorectal cancer. Diet affects a multitude of microbes responsible for physiological homeostasis, signalling of the immune system, and digesting complex polysaccharides [79–81]. Thus, examining the links between diet, microbiome, and cancer is important for understanding cancer and reducing its burden on individuals and society.

Examining cell growth in response to dietary inputs is challenging because of the difficulty of growing gut microbes in a laboratory setting. There are thousands of species of gut microbes, but only a few have been cultured in the lab [8, 82, 83, 84••]. From those that have been grown in the lab, we know the following. Plant-based diets encourage a relatively high abundance of Bacteroidetes-related taxonomic groups [85], *Lactobacillus* [85], *Bacillus polyfermenticus* [86], and *Bifidobacterium* [85] in vivo. *Bacteroides* spp. and *Bacillus polyfermenticus* inhibit the proliferation of human colon cancer cells [37, 86, 87], while *Lactobacillus* and *Bifidobacterium* inhibit the development of colorectal cancer by inhibiting gut inflammation and angiogenesis [84••].

The plant-digesting *Propionibacterium* spp. induces apoptosis in colorectal cancer cells [88]; *Faecalibacterium prausnitzii* protects from colon tumour development through their anti-inflammatory effects and production of the anti-carcinogenic metabolite butyrate [89–92]; and *Eggerthella*, *Alistipes*, and *Phascolarctobacterium* [93] have opposing effects on cancer. Although *Alistipes* and *Phascolarctobacterium* are relatively enriched in healthy volunteers, *Eggerthella* is relatively enriched in patients with colorectal cancer [33]. The mucin-digesting *Akkermansia muciniphila*, *Enterococcus hirae*, and *Bacteroides* spp. inhibit tumour development by activating immune T-cells [94–97]. Dairy products also encourage the growth of *Lactobacillus* species [84••, 98–100] and *Bifidobacterium* spp. [84••]. These microbes as well as *Eubacterium* species, *Peptostreptococcus* strain DZ2, and *Fusobacterium* strain AB are associated with a lower risk of developing colorectal cancer [101].

Microbes inhabit the guts of all multicellular organisms and have coevolved with their hosts for millions of years [79, 102–104]. Recent work has identified the gut microbiota of over 270 vertebrate species [40, 105••, 106–119]. Similar diets and/or ancestry appear to be associated with similar gut microbiota in mammals [120–124]. Herbivores and carnivores have distinct gut microbiota [125]. Firstly, herbivores have more diverse microbial populations than carnivores

[126]. In herbivores, the predominant microbial families are *Atopobiaceae*, *Barnesiellaceae*, *Defluvitaleaceae*, *Fibrobacteraceae*, *Lachnospiraceae*, *Methanocorpusculaceae*, *Oscillospiraceae*, *Rikenellaceae*, *Spirochaetaceae*, and *Synergistaceae* [127••, 128••]. In carnivores, Actinobacteria, *Bacteroidaceae*, *Clostridiaceae*, *Enterobacteriaceae*, Firmicutes, *Fusobacteriaceae*, *Peptostreptococcaceae*, and *Proteobacteria* are predominant [127••, 129]. The group of microbes associated with carnivores is more similar to a healthy human gut microbiome than the group of microbes associated with herbivores, since a healthy human gut microbiome consists of about 90% Bacteroidetes and Firmicutes [8, 12–14] and 10% Actinobacteria, *Fusobacteria*, Proteobacteria, and Verrucomicrobia [12, 15, 16]. This is somewhat counter-intuitive because diets high in meat products are associated with higher cancer risk and other health problems in humans [77, 130].

Primarily herbivorous mammalian orders, such as Rodentia, Primates, Artiodactyla, and Marsupialia, have lower malignant or benign tumour prevalence than Carnivora [3, 131]. Also, in a pilot study across nonhuman vertebrates, diet was the only life history variable which explained some of the variance in cancer prevalence. Specifically, higher trophic levels, like apex predators, had higher cancer prevalence than lower trophic levels, like herbivores. Therefore, there is a need to understand the possible role of diet-associated microbes on cancer prevalence across nonhuman vertebrates.

We Systematically Review the Effects of Diet and Microbiome on Cancer Across Nonhuman Species

In this paper, we systematically review existing work on the relationship between diet, the microbiome, and cancer across nonhuman animals. Given what is known about the relationship between dietary substrates, the microbiome, and cancer incidence in humans, we expect to find lower cancer rates in species with herbivorous-related microbes and higher cancer rates in species with carnivorous-related microbes. Revealing the diet-related oncobiome across the tree of life can help us identify model organisms possibly useful for human preclinical trials and explain the variance in cancer prevalence across species.

Methods

Review Included Keywords Relating to Diet, Microbes, and Cancer

We conducted a systematic review to identify all reported cases of the interaction between diet, microbiota, and cancer in species beyond humans. We used the Arizona State University library search engine (including, e.g. GoogleScholar, Mendeley, and JSTOR) to find articles with the following keywords: (diet* OR food* OR "trophic level*" OR herbivor* OR insectivor* OR carnivor* OR omnivore* OR eat*) AND (*gut* OR *intestin* OR digestive OR stomach OR colo*) AND (cancer* OR malignan* OR benign OR neoplas* OR tumo?r* OR metasta* OR dysplas*) AND (microb* OR bacteria OR fung* OR microorganism* OR infect* OR fecal) AND (species OR zoo* OR wild* OR host* OR animal*).

We also used the following terms in the 'NOT' argument in order to exclude irrelevant articles that appeared when using only the list of terms in the 'AND' arguments above: NOT ("clinical trial* in humans" OR "human clinical trial*" OR "mathematical model*" OR "human bod*" OR "human tissue*" OR "human cancer*" OR "human gut" OR "computer simulation*" OR "computational model*" OR radiation OR "electr* field*" OR "magnetic field*" OR "renewable energy" OR "physics of cancer*" OR "in vitro" OR "in silico" OR "light to cure cancer*" OR tribe* OR nationalit* OR tobacco OR smoking OR "alcohol intake" OR "develop* world" OR "develop* countr*" OR laser OR "societ* and culture*" OR workplace OR cook* OR "human lymph" OR "human prostate" OR "human immun*" OR "human breast" OR "human skin" OR "human colo*" OR "human trial*" OR "human myocardial" OR "human monoclonal" OR "human sarcoma" OR "phase 1 trial" OR "phase 2 trial" OR "phase 3 trial*" OR "*pregnant wom?n" OR "human leukemia*" OR "human melanoma*" OR "energy minimization" OR "information coding" OR "Markov model" OR "free energy landscape" OR superconduct* OR astrobiology OR atavis* OR anaphylax* OR heart OR cardiovascular OR respiratory OR syndrome* OR mental* OR "blood disease*" OR diabet* OR Alzheimer* OR polio* OR measles OR "Bubonic Plague" OR stroke OR "multiple sclerosis" OR "Infectious mononucleosis" OR AIDS OR HIV OR "bronchus cancer" OR "lung cancer*" OR "breast cancer*" OR bronchitis OR emphysema OR asthma OR dementia OR ethnicity OR suicide OR biophysics OR "bone homeostasis" OR "common cold" OR diphtheria OR paralysis OR coronavirus OR chickenpox OR "Huntington's disease" OR rabies OR dengue OR leprosy OR osteoporosis OR gonorrhoea OR syphilis OR "heavy metal*" OR "air pollut*" OR "genetic disease*" OR "world health organi?ation" OR airborne OR tuberculosis OR eczema OR acne OR COVID OR hemophilia OR thrombos?s).

Excluded Papers from Irrelevant Disciplines

We excluded papers from the disciplines of "arts & humanities", "Business & Economics", "Engineering",

"Law", "Library & Information Science", "Physics", "Psychology", "Social Sciences", and "Statistics", as well as reference entries, reviews, web sources, book chapters, books, conference proceedings, newspaper articles, government documents, maps, patents, audio, and videos. We only included articles written in English. This led to a total of 1,167 articles.

Included Additional Articles Through Tracing Citations and Performing Additional Searches

We also searched for additional articles by tracing citations backwards and forwards for key articles using standard methodology for doing so in systematic reviews [132]. We completed this query on the 14th of June 2021.

We then performed a separate literature search for several key publications in the fields of comparative oncology, nutritional ecology, and microbiology that mention links between diet, microbes, and cancer in nonhumans as well as humans, given that comparative oncology articles with the word "humans" may have been excluded in our above keyword search.

Excluded Papers that Were Not Relevant to Microbes, Diet, and Cancer Across Species

We screened all the studies that resulted from these searches. One co-author (S.E.K.) screened 50% of the articles starting from the oldest to the newest, and another co-author (G.M.A.) screened the remaining 50% of articles starting from the newest to the oldest, using a shared document to identify articles that had been already screened by the other person. If there was uncertainty about inclusion of certain articles, both co-authors read those articles and agreed on inclusion or exclusion. Both S.E.K. and G.M.A. reviewed (duplicate reviewed) at least 47 articles. We excluded 1,532 publications with irrelevant titles or abstracts, those mostly focused on humans, and/or papers with no descriptions of direct links between diet, microbes, and cancer (Supplementary Table; Supplementary Figure). We provide the final list of 31 included articles in Table 1. From these articles, we extracted information about the standard diet of hosts in the experiments, the route of microbial administration to the host, the microbial species, whether the microbiome was experimentally added (i.e. by the researchers) or naturally present in the host (e.g. natural gut flora), the host species, and the resulting effects on cancer incidence or progression by searching for standard dietary information of the host organism(s) in the methods sections and searching for keywords, such as cancer, malignan, benign, neoplas, tumo, metasta, and dysplas.

Results

We found that the majority of articles (27 out of 31 studies; Table 1) reporting direct associations between microbes and cancer were conducted in murine model organisms (e.g. mice). The remaining four studies were in dogs, cats, flies, and chickens. The types of tumours studied in these organisms were mostly associated with gastrointestinal tissues (colon, colorectal, midgut, rectum, antrum, liver, gastric, intestine) (~61%, i.e. 19 out of 31 studies). Fewer studies examined the effect of microbes on tumourigenesis in breast tissue (~19%, i.e. 6 out of 31 studies), the lung (1 out of 31 studies), bladder (1 out of 31 studies), multiple sites (1 out of 31 studies), brain (1 out of 31 studies), and skin or mucosa (2 out of 31 studies). Although we did not set out to focus our review on experimentally induced microbiomes, 83.8% of the studies (26 out of 31 studies) that ended up being included used experimentally induced microbiomes. The majority of microbes in Table 1 were administered orally to the hosts (20 out of 31 studies). In a few studies, hosts received microbes via subcutaneous injection [133] or aerosolisation [134]; in two studies, the microbes being studied were naturally present in the hosts [135, 136] (Table 1).

Cancer-Associated Microbes Are Found Across Several Nonhuman Species

We discovered a wide range of microbes that were consistently associated with inhibition and/or induction of cancer across nonhuman species. We identified several patterns in the way microbes affect cancer in seven different host species (Table 1), including fruit flies, chickens, mice, rats, gerbils, cats, and dogs. In all studies in Table 1 that administered *Lactobacilli* species alone, the researchers observed an inhibition of cancer, inhibition of tumour growth, or a reduction in tumour size in breast, lung, colon, and bladder tissues of mice and rats. On the other hand, in all studies in Table 1 where *Helicobacter* was present, they consistently saw induction of carcinogenesis in mice [137], tumour growth in gerbils [138], and overall dysplasia in cats [139]. Some microbes, such as *Lactobacilli* and *Clostridiales*, are associated with inhibition of cancer when they are administered as individual species, but when they are administered as part of a community of various microbial species, the overall effects on cancer are sometimes positive and other times negative (Table 1).

Table 1 Examples of microbes promoting or inhibiting tumourigenesis in nonhuman species

Microbes	Route of microbial administration	Experimentally induced or natural microbiome	Effect on cancer	Tissue	Host	Standard host diet in the experiment	References
Prevotella, *Lactobacillus*, *Treponema*, *Roseburia*, *Eubacterium*, and *Ruminococcus*	Already existing gut microbiota in the rats	Natural	Lower abundance of *Prevotella*, *Lactobacillus*, *Treponema*, *Roseburia*, *Eubacterium,* and *Ruminococcus* in rats with colorectal cancer	Colorectal	Wistar rats	"Rodent diet"	[136]
Clostridiales	Germ-free mice colonised with human faeces	Experimental	*Clostridiales* were negatively associated with tumour burden	Colon	C57BL/6 mice	N/A	[219]
Bifidobacterium bifidum	Oral	Experimental	Inhibit cancer cell growth	Colon	ApcMin/ + mice	N/A	[220]
Free of *Helicobacter* spp.	Maintained in a *Helicobacter*-free environment	Experimental	Inhibit cancer	Colon	SMAD3-deficient mice	Irradiated Picolab rodent diet 20 5053 or autoclaved rodent chow	[155]
Lactobacillus acidophilus	Oral	Experimental	Inhibit cancer	Breast	BALB/c mice	N/A	[221]
Lactobacillus brevis	Oral	Experimental	Inhibit tumour metastasis to the liver	Breast	BALB/c mice	N/A	[222]
Lactobacillus casei	Oral	Experimental	Inhibit tumour growth rate	Breast	BALB/c mice	N/A	[221]
Lactobacillus fermentum; *L. fermentum* also reduced the percentage of *Bacteroides*	Oral	Experimental	Inhibit tumour formation	Colon	ICR mice	"Standard diet"	[223•]
Lactobacillus gasseri	Oral	Experimental	Inhibit cancer cell growth	Colon	ApcMin/ + mice	N/A	[220]
Lactobacillus helveticus	Oral	Experimental	Inhibit tumour growth	Breast	BALB/c mice	"Balanced diet"	[224]
SeNP-enriched *Lactobacillus plantarum*	Oral	Experimental	Inhibit tumour growth	Breast	BALB/c mice	"Standard mouse pellet diet"	[225]
Lactobacillus plantarum LS/07A	Oral	Experimental	Inhibit tumour frequency	Breast	Sprague Dawley rats	"Conventional MP diet (Peter Miško, Snina, Slovakia)"	[226]
Lactobacillus rhamnosus	Aerosolisation	Experimental	Inhibit metastases	Lung	C57BL/6 mice	food (no description of specific diet)	[134]
Lactobacillus rhamnosus strain GG	Oral	Experimental	Inhibit tumour growth	Bladder	C57BL/6 mice	"Standard mouse diet (Glen Forrest Stockfeeders, WA, Australia)"	[227]
Lactobacillus rhamnosus strain GG	Oral	Experimental	Inhibit tumour incidence, multiplicity, and volume	Colon	Sprague Dawley rats	Food (no description of specific diet)	[228]

Table 1 (continued)

Microbes	Route of microbial administration	Experimentally induced or natural microbiome	Effect on cancer	Tissue	Host	Standard host diet in the experiment	References
Salmonella enterica with antioxidant oils	Oral	Experimental	Inhibit tumour burden	Liver	C57BL/6 mice	Ground standard mouse chow (Harlan) or meal mixed with antioxidant oil	[154]
Alistipes finegoldii, Alistipes putredinis, *Bacteroides massiliensis*, *Bacteroides rodentium*, *Bacteroides sartorii*, *Clostridium clostridioforme*, *Clostridium methylpentosum*, *Lactobacillus animalis*, *Lactobacillus murinus*, *Muribaculum intestinale*, *Oscillibacter valericigenes*, *Parasutterella excrementihominis*	Oral***	Experimental	Inhibit melanoma	Melanoma	Germ-free C57BL/6 mice	Autoclaved chow diet (LabDiet 5K67, Purina Foods)	[153]
Clostridium butyricum and *Bacillus subtilis*	Oral	Experimental	Inhibit proliferation of cancer cells	Colorectal	C57BL/6 mice	N/A	[152]
"*Lactococcus lactis*, *Lactobacillus kefiri*, *Lactobacillus plantarum*, *Lactobacillus casei*, *Lactobacillus brevis*, *Lactobacillus acidophilus*, several other bacterial strains and probiotic yeasts"	Oral	Experimental	Reduce tumour size	Breast	BALB/c mice	"Standard diet pellet"	[229]
Enterotoxigenic *Bacteroides fragilis*	Oral	Experimental	Promote tumour growth	Colon	Apc knockout mice	N/A	[148]
Enterococcus faecalis	Oral	Experimental	Promote dysplasia and adenocarcinoma	Rectum	Interleukin-10-deficient mice	N/A	[230]
Fusobacterium nucleatum	Subcutaneous injection	Experimental	Promote cancer	Colorectal	Xenograft mice	N/A	[133]
Helicobacter hepaticus	"Potentially infected"	N/A	Promote hepatocellular neoplasms and hemangiosarcomas	Liver	B6C3F1 mice	N/A	[231]
Helicobacter pylori	Oral	Experimental	Promote carcinogenesis	Gastric	C57BL/6 mice	N/A	[137]

Table 1 (continued)

Microbes	Route of microbial administration	Experimentally induced or natural microbiome	Effect on cancer	Tissue	Host	Standard host diet in the experiment	References
Helicobacter pylori	Oral*	Experimental	Promote tumour growth	Intestine	Mongolian gerbils (MGS/Sea) *Meriones unguiculatus*	N/A	[138]
Helicobacter pylori	"Were known to be infected with H. *pylori*"	Natural	Promote dysplasia	Antrum	Cats	Iams Cat Diet	[139]
Helicobacter spp.	Oral	Experimental	Promote cancer	Colon	SMAD3-deficient mice	Irradiated Picolab rodent diet 20 5053 or autoclaved rodent chow	[155]
Papillomavirus	N/A	Experimental	Promote malignant transformation	Skin or mucosa	Dogs	N/A	[140]
Peptostreptococcus anaerobius	Oral**	Experimental	Promote dysplasia	Colon	C57BL/6 mice	N/A	[156]
Polyoma virus	Injected into the host by many routes	Experimental	Promote tumour formation	Multiple sites	Immunologic immature neonate mice	N/A	[232]
Pseudomonas aeruginosa	Oral	Experimental	Predispose to dysplasia	Midgut	Ras1-mutated fruit flies *Drosophila melanogaster*	"Normal fly food"	[233]
Toxoplasma gondii	Infection	Natural	Promote glioma-like tumours	Brain	Chickens	N/A	[234]
Clostridium species, *Lactobacillus murinus*, and *Bacteroides* species	N/A	Experimental	Promote neoplasia	Gastrointestinal	INS-GAS mice on a FVB/N background	N/A	[151]
Bacteroides, *Odoribacter*, *Akkermansia, Prevotellaceae* and *Porphyromonadaceae*	Already existing gut microbiota in the mice; transfer of faeces and bedding	Experimental	Tumour-bearing mice had more *Bacteroides*, *Odoribacter*, *Akkermansia*, and fewer *Prevotellaceae* and *Porphyromonadaceae*; more and larger tumours developed in mice that received microbiota from tumour-bearing mice	Colon	C57BL/6mice	"Autoclaved chow diet"	[135]
Bacteroides, *Parabacteroides*, *Alistipes*, and *Akkermansia*	Germ-free mice colonised with human faeces	Experimental	*Bacteroides*, *Parabacteroides, Alistipes*, and *Akkermansia* were associated with increased tumour burden	Colon	C57BL/6 mice	N/A	[219]

Table 1 (continued)

Microbes	Route of microbial administration	Experimentally induced or natural microbiome	Effect on cancer	Tissue	Host	Standard host diet in the experiment	References
Proteobacteria, *Desulfovibrio*, *Erysipelotrichacea*, and *Fusobacterium*	Already existing gut microbiota in the rats	Natural	Higher abundance of Proteobacteria, *Desulfovibrio*, *Erysipelotrichacea*, and *Fusobacterium* in rats with colorectal cancer	Colorectal	Wistar rats	"Rodent diet"	[136]

Columns show the microbes examined, the route of microbial administration, whether the microbiome was experimentally added or naturally present in the host, the cancer-promoting or -inhibiting effect of the microbes, the type of tissue affected in terms of cancer, the host, the standard host diet if mentioned in each article, and the associated literature. Apc refers to the adenomatous polyposis coli gene. ApcMin/+ mice have a point mutation in the murine homolog of the APC gene which induce tumours in these mice. Xenograft mice are models with existing neoplasias used to study cancer and cancer therapies. B6C3F1 mice are large mice created by breeding together a C3H mouse and a C57BL/6 mouse. MGS/Sea is a strain from Seac Yoshitomi. SMAD3 is a protein-coding gene related to tumour growth. SeNP-enriched means that the bacteria were enriched with selenium nanoparticles. Ras1 is a gene related to cell growth. BALB/*c* and C57BL/6 mice are laboratory-bred, inbred strains of house mice. ICR refers to the Institute of Cancer Research. INS-GAS mice are insulin-gastrin transgenic model organisms. The FVB/N background means that these mice are susceptible to the Friend leukaemia virus B

*the gerbils were pathogen-free prior to infection with *Helicobacter pylori*; **Mice were given broad-spectrum antibiotics prior to infection; ***Mice were treated with antibiotics prior to tumour inoculation

Lactobacilli Bacteria Are Protective Against Cancer in Many Species

Lactobacillus is a microbe that is beneficial to many host species, as it protects from colorectal cancer in humans [84••, 98–100], as well as breast, lung, colon, and bladder cancer in mice and rats (Table 1). *Lactobacilli* provide cancer protection by inhibiting cell proliferation, inflammation and angiogenesis, inactivating carcinogenic compounds, and inducing apoptosis [84••, 99, 100].

Some Microbes Have Cancer-Promoting Effects Across Species

Papillomaviruses have cancer-inducing effects in both humans [38] and dogs (Table 1). They induce skin or mucosal malignancies by integrating their genome into the host cells [140], and then, their proteins dysregulate pathways of host cell division and DNA damage/stress response [141].

Bacteroides fragilis and *Fusobacterium nucleatum* are associated with cancer in both humans [23–25, 33, 34] and mice (Table 1). *B. fragilis* induces malignancies by producing reactive oxygen species and toxins that damage the host DNA and degrade the cell-to-cell adhesion protein E-cadherin, respectively [142–144]. *F. nucleatum* induces tumourigenesis by entering host cells and promoting their own and the host cells' proliferation, as well as producing toxins that alter the adhesion and epigenetics of host cells [64, 133, 144–146].

Some Microbial Species Have Context-Dependent Effects on Cancer

Through our systematic review, we discovered that some microbes have cancer protective effects in some contexts and cancer-promoting effects in others. This makes it difficult to draw broad conclusions about the nature of the oncobiome, just as it is difficult to make broad claims about the gut microbiome across species more generally [120, 124, 127••, 147•]. For example, *B. fragilis* can have harmful effects [142, 148] or beneficial effects (reducing colitis and having an indirect effect of reducing cancer) [149] depending on the diet of the host. When *B. fragilis* has cancer-protective effects, this may be due the result of anti-inflammatory properties of soluble fibres in the host's diet [150].

In other experiments, *Clostridium* species have paradoxical effects on cancer: promoting gastrointestinal neoplasia in INS-GAS mice on a FVB/N background [151], but inhibiting proliferation of colorectal cancer cells in C57BL/6 mice [152] and inhibiting melanoma in germ-free C57BL/6 mice

[153]. *Bacteroides* species also have context-dependent effects: promoting gastrointestinal neoplasia in INS-GAS mice on a FVB/N background [151], but inhibiting melanoma in germ-free C57BL/6 mice [153] (Table 1). The different effects of *Clostridium* and *Bacteroides* species on cancer could be a result of the experiments using different strains of mice with different starting microbiomes or a number of other factors including the hosts' diet in the experiments (e.g. autoclaved chow diet [153]; diets not reported in the studies [151, 152]), sex, and age.

Many Studies Did Not Report the Diets of Animal Subjects

Unfortunately, only 15 of 31 studies in Table 1 report the standard diet that hosts were exposed to. Out of these cases, a standard/balanced rodent or cat diet was most often used, but 13 cases do not mention the company from which this food was purchased or the exact ingredients and/or nutrients of this food (Table 1). Even when studies report that food was supplied by a specific company, such as Harlan [154], we do not know whether the food supplied by these companies was specifically designed or custom-made for the study [154]. We only know the ingredients of the animals' diets in two studies. The irradiated Picolab 20 5053 rodent diet [155] mainly consists of at least 20% crude protein and 4.5% crude fat, and not more than 6% of crude fibre and 7% ash (Picolab). The LabDiet 5K67 rodent diet [153] mainly consists of at least 18% crude protein and 6% crude fat, and not more than 5% crude fibre and 8% ash (LabDiet JL). In some cases, the diet was autoclaved [153] and mixed with antioxidant oils [154], or antibiotics were given to the host prior to infection [153, 156], in order to estimate the direct effect of the newly administered microbes on cancer in the host.

Discussion

The idea that food affects health is an ancient idea. This was stated by Hipocrates in ancient Greece as "Let food be thy medicine and medicine be thy food" and is also clear in the "homology of medicine and food" in Chinese medicine [157]. Although this idea is ancient, it has important implications for modern medicine, which often neglects the critical role of diet in shaping the overall health and well-being [158–160]. Dietary interventions [161, 162] are a promising tool to prevent cancers across species given that they are safe, easily modifiable, readily accessible, and economical [163, 164].

In this review, we have identified microbial species that have a cancer-promoting and/or cancer-inhibiting effect across several hosts (Table 1). *Lactobacilli* are consistently associated with cancer inhibition (when studies did not include other microbes), and *Helicobacter* bacteria are consistently associated with cancer, across host species. However, in the presence of other microbes, *Lactobacilli* and *Clostridiales* were sometimes associated with cancer and other times associated with inhibition of cancer (Table 1). Some experiments provide dietary information, but others do not, thus highlighting the need for further systematic studies on the direct links between diet, microbes, and cancer across species that take into account the many factors that can influence the microbiome.

Carnivorous Diets May Be Associated with Cancer-Inducing Microbes

Comparative oncology studies show that within mammals, the order Carnivora has higher benign or malignant tumour prevalence than other primarily herbivorous mammalian orders [3, 131]. Also, our group has been investigating the cancer prevalence of species at different trophic levels, including carnivores, herbivores, insectivores, and others. Our preliminary results across vertebrate species show that lower trophic levels (such as herbivores) have lower cancer prevalence than higher trophic levels (such as secondary carnivores) (Kapsetaki et al. in prep). A possible explanation for this higher cancer prevalence in higher trophic levels (i.e. carnivores) may be their diet-associated oncobiome, including their lower microbial diversity than herbivores [126]. There are other distinct features of carnivore microbes that might predispose them to cancer. For example, *Fusobacteria* and *Peptostreptococcus* bacteria have tumour-inducing properties in both humans [35] and mice (Table 1) and are most abundant in carnivorous species [127••, 129]. Similarly, humans and macaques fed a cancer-associated Western diet had lower microbial diversity compared with humans who were fed fermented foods or macaques who were fed Mediterranean diet [72, 165–167].

Litter Size Might Affect Cancer Susceptibility via the Microbiome

The association of individual *Lactobacilli* species with cancer inhibition (Table 1) could be one of the reasons behind the observation of higher cancer prevalence in mammals of larger litter size [168••]. It is reasonable to speculate that mammals with larger litter size likely have lower parental investment in general because they are characterised by a faster life history strategy [169]. Mammalian species with larger litter size often have shorter gestation length [170], an indicator of parental investment. Although we were not able to find reports of shorter lactation length or less milk being transferred to each offspring, it is possible that species with larger litter sizes are transferring less milk and therefore

cultivate fewer *Lactobacillus* bacteria in their offspring. This is one hypothesis that could be tested for why higher cancer prevalence has been observed in species of larger litter size [168••]. Future work should test whether there is an association between litter size and *Lactobacillus* prevalence.

Helicobacter Bacteria Have Cancer-Promoting Effects and Could Be a Transmissible Carcinogen

Helicobacter bacteria are often linked with the development of cancers in humans [27, 30, 171], as well as carcinogenesis in mice [137], tumour growth in gerbils [138], and overall dysplasia in cats [139] (Table 1). *Helicobacter* bacteria secrete VacA toxins which create pores in host cells and a cascade of intracellular events leading to host cell apoptosis [172]. *Helicobacter* bacteria also attach to and align their growth with host cells; this allows *Helicobacter* to pass CagA toxins inside the host cells [64, 173, 174]. CagA toxins rewire the host cells' gene expression, induce inflammation and oxidative stress, and alter host cell polarity, which are associated with a high risk of developing gastric and colorectal cancers [27, 173, 174].

The fact that *Helicobacter* bacteria induce cancers in mice, gerbils, cats (Table 1), and humans [30, 171] raises the possibility that *Helicobacter* could be a transmissible agent that increases the risk of cancer across species from one trophic level to the next when one species (e.g. a cat) consumes another (e.g. a mouse). However, further research is necessary to test this hypothesis.

Limitations and Future Directions

The microbiome is a complex network and there are still many unknowns. The composition of the gut microbiome can vary interindividually [175], with age [51], by sex [52, 176], and even between animals sampled from the wild or in captivity [177–180]. It will be important to control for species age and sex when drawing links between diet, microbes, and cancer across species. In addition, there are many microbes with contradictory effects on cancer in different studies [142, 148, 149, 151–153]. Identifying the mechanistic links between these microbes and the hosts' respective diets will be an important next step.

Studying Underlying Mechanisms Is Key to Establishing Causal Relationships Among Diet, Microbes, and Cancer

A causal link between microbes and tumour proliferation has been identified in several microbes such as *F. nucleatum*, enterotoxic *Bacteroides fragilis*, *E. faecalis*, *Peptostreptococcus anaerobius*, *Helicobacter pylori*, and human papillomaviruses [38, 163, 181]. However, whether the correlation, for example, between *Proteobacteria*, *Desulfovibrio*, *Erysipelotrichacea*, and *Fusobacterium* abundance and colorectal cancer in rats is causal is not entirely clear [136]. *Proteobacteria* interact with intestinal cells via type III bacterial secretion systems [182]. *Desulfovibrio* produces hydrogen sulphide which can lead to DNA damage [183, 184]. *Fusobacterium nucleatum* promotes the expression of mucin and the proinflammatory cytokine tumour necrosis factor alpha [185] tumourigenesis by entering host cells, altering their proliferation and attachment to neighbouring cells [64, 133, 144–146]. However, in the majority of microbial-cancer associations (e.g. Table 1), it is unknown whether the relationship is causal, one-/bi-directional, or mere correlation [38, 162, 186].

Studying the mechanisms that underlie the relationships among diet, microbes, and cancer is necessary to better understand the causal relationships among these variables. For example, mechanisms like resource availability/limitation in the gut, inflammation, the production of growth factors, and even cell signalling between microbes and cancerous/precancerous cells [187–189] are all potential mechanisms that might underlie these links.

Most Microbial Species in the Gut Microbiome Are Still Unknown

Another limitation that must be acknowledged is that the vast majority of species in the microbiome are still unknown. Even though advances in metagenomics have enabled the sequencing of 806 microbial genomes across 124 humans [15], and 5,000 microbial genomes across approximately 180 wild and captive species [126], there is still insufficient genome coverage for many microbial genomes that are underrepresented in the gut microbiome. Further, it is difficult to reconstruct repetitive and low complexity genomic regions with short-read based methodological approaches [126, 190], and 99% of species in the gut microbiome still cannot be cultured [84••]. Researchers estimate that there are trillions of microbial species that are yet to be observed [10].

Host Ecology and Physiology Influences the Composition of the Microbiome

The ecology and physiology of the hosts [191–194] may also influence the taxonomic abundance and diversity of their microbiome [56, 195–200]. Environments with scarce amounts of plants and high abundance of prey animals favour the evolution of carnivory over herbivory [201]. Therefore, the distinct microbiome of a habitat may affect an animals' microbiome. Also, there may be unique microbial niches in carnivores versus herbivores as a result of

phenotypic differences in how these animals eat and digest food. Researchers have suggested that canine teeth, large mouth openings, short digestive tracts, lower pH in the stomach, sharp claws, and nocturnal living [202–205] may create favourable niches for pathogenic microbes, whereas wide flat teeth, small mouth openings, larger and longer digestive tracts, higher pH in the stomach, flattened nails or blunt hooves, and diurnal living [202, 205–212] might create favourable niches for microbes that have more positive effects on health. Future work can and should explore whether these phenotypes influence the viability of cancer-promoting and cancer-inhibiting microbes.

Microbiome and Diet Interventions Could Reduce the Burden of Cancer Across Species

By utilising what we know about the role of the microbiome, diet, and cancer, it should be possible to better diagnose, prevent, and treat cancers across species. Plant-based and dairy diets are associated with a decreased cancer risk [213]. Both of these diets encourage the growth of *Lactobacillus* species [84••, 85, 98–100]. Therefore, the association of *Lactobacilli* with cancer inhibition across several host species may be tightly linked with and able to be manipulated by diet. Interventions such as dietary therapies, dietary-induced microbial therapies, probiotics and prebiotics, microbial biomarkers, and personalised medicine, have proven to be effective for decades [157, 214–216]. Future studies should test diet- and microbial-based therapies across species to help reduce the burden of cancer in nonhuman animals and can also help discover new treatments that could be used in humans.

Zoos Provide an Opportunity for Future Research

Most of the studies summarised in Table 1 use mice and rats. Although mice and rats are widely understood and well-studied in the lab, there are limitations to studies using them exclusively. Differences in cancer phenotype, tumour origins, and tumour karyotypes between humans and mice highlight some of the many phylogenetic complexities of trying to understand global patterns of comparative oncology and their links with diet and microbes [217]. Broadening this range of hosts to many other species is a key step towards untangling the complex phylogenetic relationships between diet, microbes, and cancer across species.

Most studies in Table 1 are experimental, meaning the microbes were experimentally administered to the host rather than naturally observed in the microbiome. This introduces potential bias because current knowledge may not correlate with naturally occurring microbiomes. Although these studies are good for observing correlations between certain microbes and cancer, they do not look for correlations between common diets and cancer progression. In order to overcome the limitations of experimental mouse models, the next step would involve quantifying the effect of diet and microbes on cancer across species in captive environments such as zoos. Since zoos regularly track the diet of their animals, it would be simpler to test for links between specific diets and microbes via metagenomic analyses of faecal microbiomes. These data could then be compared with cancer data from already existing cancer records in the zoos [168••, 218] to identify how diet changes the microbiome and reduces cancer incidence, particularly in species prone to cancer.

Conclusions

We discovered several broad patterns in this review of diet, microbiome, and cancer. Some microbes, such as *Helicobacter* bacteria, papillomaviruses, and the carnivore-associated *Fusobacteria*, consistently induce tumourigenesis in humans and other species, and some microbes, such as the milk-associated *Lactobacillus*, consistently inhibit tumourigenesis in humans and other species (Table 1).

Identifying the diet-related oncobiome across the tree of life may enable us to use new model organisms for preclinical trials, better understand cancer across species, and develop universal diagnostic, prevention, and treatment regimes to fight cancer and improve animal welfare. The advent of high-throughput sequencing and multi-institutional collaborations between evolutionary biologists, veterinary nutritionists, and pathologists makes these goals entirely possible.

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Author Contribution A.A. conceived the idea for this review. S.E.K. and G.M.A designed, structured, and gathered the data for the systematic review and wrote the first draft. C.C.M., C.M.W., and A.A. provided guidance during the project. All authors discussed and contributed to the final versions of the manuscript.

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Data Availability We provide all data in the supplementary table.

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universities where the research was performed or the National Institutes of Health.

Compliance with Ethical Standards

Consent for Publication All authors have given their consent for publication.

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• Of importance
•• Of major importance

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