

Diet, microbes, and cancer across the tree of life: a systematic review

Stefania E. Kapsetaki (✉ skapseta@asu.edu)

Arizona State University

Gissel Marquez Alcaraz

Arizona State University

Carlo C. Maley

Arizona State University

Corrie M. Whisner

Arizona State University

Athena Aktipis

Arizona State University

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Diet, microbes, and cancer across the tree of life: a systematic review

Authors

Stefania E. Kapsetaki^{1,2,+ #}, Gissel Marquez Alcaraz^{1,2,+}, Carlo C. Maley^{1,2}, Corrie M.

Whisner^{3,4*}, Athena Aktipis^{1,5*}

+ co-first authors

* co-senior authors

corresponding author

Author affiliations

¹ Arizona Cancer Evolution Center, Biodesign Institute and School of Life Sciences, Arizona State University, Tempe, AZ, U.S.A.

² Biodesign Center for Biocomputing, Security and Society, Arizona State University, Tempe, U.S.A.

³ College of Health Solutions, Arizona State University, Phoenix, AZ 85004, U.S.A.

⁴ Biodesign Center for Health Through Microbiomes, Arizona State University, Tempe, AZ, U.S.A.

⁵ Department of Psychology, Arizona State University, Tempe, AZ, U.S.A.

Abstract

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. We systematically reviewed over a thousand published articles and identified links between diet, microbes and cancers in several species of mammals, birds, and flies. Some microbes, specifically *Fusobacteria*, *Bacteroides fragilis*, *Helicobacter* bacteria, and papillomaviruses, have cancer-inducing effects in gerbils, mice, dogs, or cats. Other microbes, such as *Lactobacillus* species, mostly found in milk products, prevent gastrointestinal, breast, and lung cancers in mice and rats. Future work should examine a larger variety of host species to discover new model organisms for human preclinical trials, better understand the observed variance in cancer prevalence across species, and 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, trophic levels, tumour, probiotic

Background

Cancers are 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 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 across species. We begin with a brief overview of what is known about the human microbiome, diet and cancer. Then we discuss our findings about cancer across species and place this information in the broader context of human cancers.

Gut microbes and hosts have been co-evolving for millions of years

Microbes inhabit the guts of all known multicellular organisms, and have coevolved with their hosts for millions of years [4–7]. Their interaction with their hosts depends on many aspects of the external and internal environment. Dietary intake [8–11], drug exposures [11–14], host genetics [15–18], age [19], gender [20], lifestyle [21, 22], group living arrangements [23–25], and contact with soil [26–28], influence the gut microbiome. Diet is a key modulator of the gut microbiome and host tissue [9, 11, 22, 28–31], affecting the development of diseases such as cancer [32–34].

Diets low in animal products are cancer-protective

Specific diets have been linked with cancer in humans [32–35], with those rich in fibre, fruits, yoghurts, whole grains, extra virgin olive oil, vegetables, and low in animal products conveying cancer-protection [36–41] (Figure 1). On the other hand, highly-processed food [42, 43], animal fats, red meat, and low intakes of dietary fiber are known to

increase the risk of cancer [44, 45] (Figure 1). Western diet-related microbial dysbiosis [46] also drives colorectal cancer. Diet affects a multitude of microbes responsible for physiological homeostasis, signalling of the immune system, and digesting complex polysaccharides [4, 47, 48]. Thus, examining the links between diet, microbiome and cancer are important for understanding cancer and reducing its burden on individuals and society.

Healthy human microbiomes include largely Bacteroidetes and Firmicutes

The gut microbiome is the entire population of microbes inhabiting the gut [49, 50]. 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 [51–56]. In healthy individuals, approximately 90% of our gut microbes belong to the phyla Bacteroidetes and Firmicutes [53, 57–59]. The remaining 10% are Actinobacteria, *Fusobacteria*, Proteobacteria, and Verrucomicrobia [57, 60, 61].

Plant- and milk-based diets encourage growth of cancer-protective microbes

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 that have been cultured in the lab [53, 62–64]. 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 [65], *Lactobacillus* [65], *Bacillus polyfermenticus* [66], and *Bifidobacterium* [65] *in vivo*. *Bacteroides spp.* and *Bacillus polyfermenticus* inhibit the proliferation of human colon cancer cells [66–68], while

Lactobacillus and *Bifidobacterium* inhibit the development of colorectal cancer by inhibiting gut inflammation and angiogenesis [64].

The plant-digesting *Propionibacterium spp.* induce apoptosis in colorectal cancer cells [69], *Faecalibacterium prausnitzii* protect from colon tumour development through their anti-inflammatory effects and production of the anti-carcinogenic metabolite butyrate [70–73], and *Eggerthella*, *Alistipes*, and *Phascolarctobacterium* [74] have opposing effects on cancer. Although *Alistipes* and *Phascolarctobacterium* are relatively enriched in healthy volunteers, *Eggerthella* are relatively enriched in patients with colorectal cancer [75]. The mucin-digesting *Akkermansia muciniphila*, *Enterococcus hirae*, and *Bacteroides spp.* inhibit tumour development by activating immune T-cells [76–79]. Dairy products also encourage the growth of *Lactobacillus* species [64, 80–82] and *Bifidobacterium spp.* [64]. These microbes as well as *Eubacterium* species, *Peptostreptococcus* strain DZ2, and *Fusobacterium* strain AB are associated with a lower risk of colorectal cancer [83].

Gut microbes are associated with colorectal cancer

The oncobiome [84], 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) [85]. An underrepresentation of species within the *Escherichia*, *Citrobacter*, *Shigella*, *Flavobacterium*, *Acinetobacter*, and *Chryseobacterium* genera has been noted in tumour tissues of patients with colorectal cancer [86]. A low relative abundance of *Lachnospiraceae* species, *Bifidobacterium animalis* and *Streptococcus thermophilus* [87, 88], and a relatively high abundance of *Bacteroides clarus*, *Roseburia intestinalis*, *Clostridium hathewayi* [89], *Fusobacterium nucleatum* [90–92], *Parvimonas micra*, and *Solobacterium moorei* serve as biomarkers of colorectal cancer [93]. Infection with *Helicobacter pylori* bacteria positive for the CagA protein is associated with an increased risk of developing colorectal

adenocarcinoma [94]. Bacteremia from *Clostridium septicum* increases the risk of developing colorectal cancer [95]. Firmicutes and *Lactococcus* are more abundant in the gut microbiota of colorectal cancerous tissues versus neighbouring colorectal non-cancerous tissues [96]. *Helicobacter hepaticus* promotes the development of toxin- and virus-induced hepatocellular carcinoma [97]. *Clostridium difficile* [98, 99], *Enterococcus faecalis*, *Bacteroides fragilis*, *Escherichia coli*, *Streptococcus bovis/gallolyticus* [75, 100], *Porphyromonas*, *Peptostreptococcus*, *Gemella*, *Mogibacterium*, *Klebsiella* [101], and *Prevotella* [102] are relatively more abundant in patients with colorectal cancer than healthy individuals.

The fact that some microbes within the *Bacteroides* [68, 75, 89, 100] and *Bifidobacterium* taxa [87, 88] 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 associated with other cancer types

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 [97]. *Helicobacter pylori*, hepatitis B virus, and human papillomaviruses drive gastric, hepatic, and cervical cancers [103]. *Helicobacter pylori* is also associated with lymphoma, prostate cancer, sarcoma, and pancreatic cancer, via several mechanisms including the regulation of inflammatory and endocrine pathways [104].

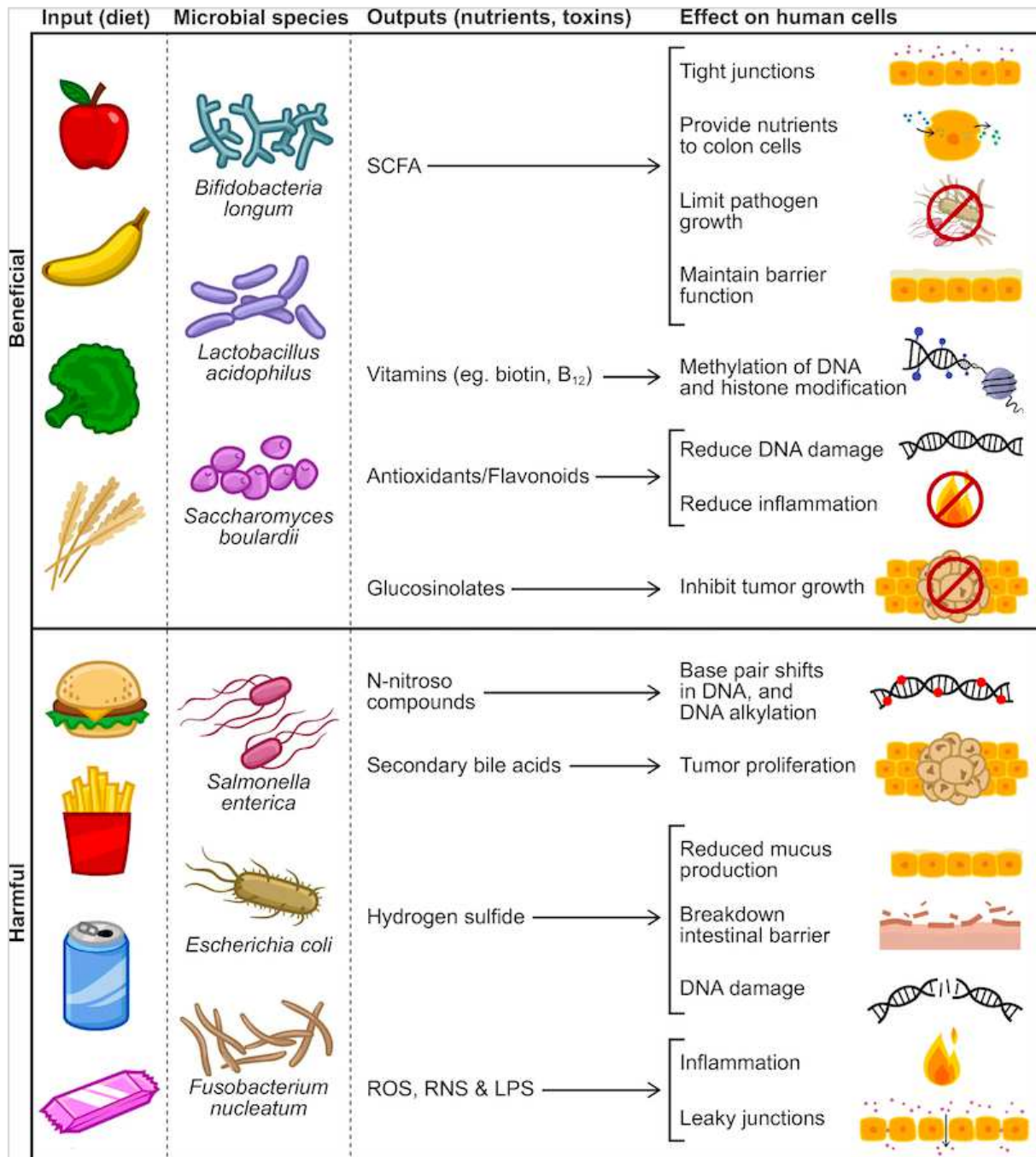


Figure 1. Examples of the effect of specific diets on microbes and cancer in humans.

Some of the microbial-associated metabolites in this figure are short-chain fatty acids

(SCFA), reactive oxygen species (ROS), lipopolysaccharide (LPS), and reactive nitrogen

species (RNS). This figure has been reproduced unchanged from Whisner and Aktipis [32] (Open Access: Creative Commons Attribution 4.0 International License, <http://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, distribution, and reproduction in any medium.

Herbivores and carnivores have distinct gut microbiomes

Recent work has identified the gut microbiota of over 270 vertebrate species [8, 105–119]. Herbivores and carnivores have distinct gut microbiota [120]. Firstly, herbivores have more diverse microbial populations than carnivores [121]. In herbivores, the predominant microbial families are *Atopobiaceae*, *Barnesiellaceae*, *Defluvitaleaceae*, *Fibrobacteraceae*, *Lachnospiraceae*, *Methanocorpusculaceae*, *Oscillospiraceae*, *Rikenellaceae*, *Spirochaetaceae*, and *Synergistaceae* [122, 123]. In carnivores Actinobacteria, *Bacteroidaceae*, *Clostridiaceae*, *Enterobacteriaceae*, Firmicutes, *Fusobacteriaceae*, *Peptostreptococcaceae*, and *Proteobacteria* are predominant [122, 124]. 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 [53, 57–59], and 10% Actinobacteria, *Fusobacteria*, *Proteobacteria*, and *Verrucomicrobia* [57, 60, 61]. This is somewhat counter-intuitive because diets high in meat products are associated with higher cancer risk and other health problems in humans [45, 125].

Similar diets and/or ancestry appear to be associated with similar gut microbiota in mammals [126–130]. Primarily herbivorous mammalian orders, such as Rodentia, Primates, Artiodactyla, and Marsupialia, have lower malignant or benign tumour prevalence than Carnivora [3, 131].

We systematically review the effects of diet and microbiome on cancer across 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 microbiome across the tree of life can help us identify model organisms possibly useful for human preclinical trials, explain the variance in cancer prevalence across species, and potentially help us discover dietary, prebiotic, and probiotic approaches to diagnose, prevent, and treat cancers in humans, zoo animals, domestic pets and wildlife.

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 tumor* OR metastas* OR dysplas*) AND (microb* OR bacteria OR fung* OR microorganism* OR infect* OR fecal) AND (species OR zoo* OR wild* OR host* OR

animal*), 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 key-word search.

Excluded papers that were not relevant to microbes, diet, and cancer across species

We screened all the studies that resulted from these searches and 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). We provide the final list of 31 included articles in Table 1, including 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- or naturally-induced, the host species, and the resulting effects on cancer incidence or progression.

Studies mostly used experimentally-induced microbiomes

Although we did not set out to focus our review on experimentally-induced microbiomes, most of the studies that ended up being included used experimentally-induced microbiomes. The majority of microbes in Table 1 were administered orally to the hosts, with few hosts receiving the microbes via subcutaneous injection [133] or aerosolization [134], and other examined microbes being naturally present in the hosts [135, 136] (Table 1).

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 [137], we do not know whether the food supplied by these companies was specifically designed or custom-made for this study [137]. We only know the ingredients of the animals' diets in two studies. The irradiated Picolab 20 5053 rodent diet [138] mainly consists of at least 20% crude protein and 4.5% crude fat, and not more than 6% of crude fiber and 7% ash (Picolab). Whereas the LabDiet 5K67 rodent diet [139] mainly consists of at least 18% crude protein and 6% crude fat, and not more than 5% crude fiber and 8% ash (LabDiet JL). In some cases the diet was autoclaved [139], mixed with antioxidant oils [137], or antibiotics were given to the host prior to infection [139, 140],

in order to estimate the direct effect of the newly administered microbes on cancer in the hosts.

Results

Cancer-associated microbes are found across several nonhuman species

We discovered a wide range of microbes with cancer-protective and/or cancer-inducing effects 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. Some microbes consistently show a cancer-protective or cancer-inducing effect across several host species (Table 1). *Lactobacilli* protect mice and rats from breast, lung, colon, and bladder cancer. On the other hand, *Helicobacter* consistently induce carcinogenesis in mice [141], tumour growth in gerbils [142], and overall dysplasia in cats [143]. Some microbes, such as *Lactobacilli* and *Clostridiales*, show a context-dependent effect, being cancer-protective as individual microbial species but having an overall cancer-protective or cancer-inducing effect in the presence of other bacterial species (Table 1).

Table

Table 1. Examples of microbes promoting or inhibiting tumourigenesis in nonhuman species. 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. Green rows indicate that the microbe is associated with cancer-protective mechanisms, while magenta rows indicate associations with cancer-inducing mechanisms. *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 leukemia 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.

Microbes	Route of microbial administration	Experimentally-induced or natural microbiome	Effect on cancer	Tissue	Host	Standard host diet in the experiment	References
<i>Prevotella</i> , <i>Lactobacillus</i> , <i>Treponema</i> , <i>Roseburia</i> , <i>Eubacterium</i> , and <i>Ruminococcus</i>	already existing gut microbiota in the rats	natural	lower abundance of <i>Prevotella</i> , <i>Lactobacillus</i> , <i>Treponema</i> , <i>Roseburia</i> , <i>Eubacterium</i> , and <i>Ruminococcus</i> in rats with colorectal cancer	colorectal	Wistar rats	“rodent diet”	[136]
<i>Clostridiales</i>	germ-free mice colonised with human feces	experimental	<i>Clostridiales</i> were negatively associated with tumour burden	colon	C57BL/6 mice	N/A	[244]
<i>Bifidobacterium bifidum</i>	oral	experimental	inhibit cancer cell growth	colon	ApcMin/+ mice	N/A	[245]
free of <i>Helicobacter</i> spp.	maintained in a <i>Helicobacter</i> -free environment	experimental	inhibit cancer	colon	SMAD3-deficient mice	irradiated Picolab rodent diet 20 5053 or autoclaved rodent chow	[138]
<i>Lactobacillus acidophilus</i>	oral	experimental	inhibit cancer	breast	BALB/c mice	N/A	[246]
<i>Lactobacillus brevis</i>	oral	experimental	inhibit tumour	breast	BALB/c	N/A	[247]

			metastasis to the liver		mice		
<i>Lactobacillus casei</i>	oral	experimental	inhibit tumour growth rate	breast	BALB/c mice	N/A	[246]
<i>Lactobacillus fermentum</i> ; <i>L. fermentum</i> also reduced the percentage of <i>Bacteroides</i>	oral	experimental	inhibit tumour formation	colon	ICR mice	“standard diet”	[248]
<i>Lactobacillus gasseri</i>	oral	experimental	inhibit cancer cell growth	colon	ApcMin/+ mice	N/A	[245]
<i>Lactobacillus helveticus</i>	oral	experimental	inhibit tumour growth	breast	BALB/c mice	“balanced diet”	[249]
SeNP-enriched <i>Lactobacillus plantarum</i>	oral	experimental	inhibit tumour growth	breast	BALB/c mice	“standard mouse pellet diet”	[250]
<i>Lactobacillus plantarum</i> LS/07A	oral	experimental	inhibit tumour frequency	breast	Sprague Dawley rats	“conventional MP diet (Peter Miško, Snina, Slovakia)”	[251]
<i>Lactobacillus rhamnosus</i>	aerosolization	experimental	inhibit metastases	lung	C57BL/6 mice	food (no description of specific diet)	[134]
<i>Lactobacillus rhamnosus</i> strain GG	oral	experimental	inhibit tumour growth	bladder	C57BL/6 mice	“standard mouse diet (Glen Forrest Stockfeeders, WA, Australia)”	[252]
<i>Lactobacillus rhamnosus</i> strain GG	oral	experimental	inhibit tumour incidence, multiplicity and volume	colon	Sprague Dawley rats	food (no description of specific diet)	[253]

<i>Salmonella enterica</i> with antioxidant oils	oral	experimental	inhibit tumour burden	liver	C57BL/6 mice	ground standard mouse chow (Harlan) or meal mixed with antioxidant oil	[137]
<i>Alistipes finegoldii</i> , <i>Alistipes putredinis</i> , <i>Bacteroides massiliensis</i> , <i>Bacteroides rodentium</i> , <i>Bacteroides sartorii</i> , <i>Clostridium clostridioforme</i> , <i>Clostridium methylpentosum</i> , <i>Lactobacillus animalis</i> , <i>Lactobacillus murinus</i> , <i>Muribaculum intestinale</i> , <i>Oscillibacter valericigenes</i> , <i>Parasutterella excrementihominis</i>	oral***	experimental	inhibit melanoma	melanoma	germ-free C57BL/6 mice	autoclaved chow diet (LabDiet 5K67, Purina Foods)	[139]
<i>Clostridium butyricum</i> and <i>Bacillus subtilis</i>	oral	experimental	inhibit proliferation of cancer cells	colorectal	C57BL/6 mice	N/A	[156]
“ <i>Lactococcus lactis</i> , <i>Lactobacillus kefir</i> , <i>Lactobacillus plantarum</i> , <i>Lactobacillus casei</i> , <i>Lactobacillus brevis</i> , <i>Lactobacillus acidophilus</i> , several other bacterial strains and probiotic yeasts”	oral	experimental	reduce tumour size	breast	BALB/c mice	“standard diet pellet”	[254]
enterotoxigenic <i>Bacteroides fragilis</i>	oral	experimental	promote tumour growth	colon	Apc knockout	N/A	[152]

					mice		
<i>Enterococcus faecalis</i>	oral	experimental	promote dysplasia and adenocarcinoma	rectum	Interleukin-10-deficient mice	N/A	[255]
<i>Fusobacterium nucleatum</i>	subcutaneous injection	experimental	promote cancer	colorectal	xenograft mice	N/A	[133]
<i>Helicobacter hepaticus</i>	“potentially infected”	N/A	promote hepatocellular neoplasms and hemangiosarcomas	liver	B6C3F1 mice	N/A	[256]
<i>Helicobacter pylori</i>	oral	experimental	promote carcinogenesis	gastric	C57BL/6 mice	N/A	[141]
<i>Helicobacter pylori</i>	oral*	experimental	promote tumour growth	intestine	Mongolian gerbils (MGS/Sea) <i>Meriones unguiculatus</i>	N/A	[142]
<i>Helicobacter pylori</i>	“were known to be infected with <i>H. pylori</i> ”	natural	promote dysplasia	antrum	cats	Iams Cat Diet	[143]
<i>Helicobacter</i> spp.	oral	experimental	promote cancer	colon	SMAD3-deficient mice	irradiated Picolab rodent diet 20 5053 or autoclaved rodent chow	[138]

papillomavirus	N/A	experimental	promote malignant transformation	skin or mucosa	dogs	N/A	[144]
<i>Peptostreptococcus anaerobius</i>	oral**	experimental	promote dysplasia	colon	C57BL/6 mice	N/A	[140]
polyoma virus	injected into the host by many routes	experimental	promote tumour formation	multiple sites	immunologic immature neonate mice	N/A	[257]
<i>Pseudomonas aeruginosa</i>	oral	experimental	predispose to dysplasia	midgut	Ras1 mutated fruit flies <i>Drosophila melanogaster</i>	“normal fly food”	[258]
<i>Toxoplasma gondii</i>	infection	natural	promote glioma-like tumours	brain	chickens	N/A	[259]
<i>Clostridium</i> species, <i>Lactobacillus murinus</i> , and <i>Bacteroides</i> species	N/A	experimental	promote neoplasia	gastrointestinal	INS-GAS mice on a FVB/N background	N/A	[155]
<i>Bacteroides</i> , <i>Odoribacter</i> , <i>Akkermansia</i> , <i>Prevotellaceae</i> and <i>Porphyromonadaceae</i>	already existing gut microbiota in the mice; transfer of	experimental	tumour-bearing mice had more <i>Bacteroides</i> , <i>Odoribacter</i> , <i>Akkermansia</i> , and	colon	C57BL/6 mice	“autoclaved chow diet”	[135]

	feces and bedding		fewer <i>Prevotellaceae</i> and <i>Porphyromonadaceae</i> ; more and larger tumours developed in mice that received microbiota from tumour-bearing mice				
<i>Bacteroides</i> , <i>Parabacteroides</i> , <i>Alistipes</i> , and <i>Akkermansia</i>	germ-free mice colonised with human feces	experimental	<i>Bacteroides</i> , <i>Parabacteroides</i> , <i>Alistipes</i> , and <i>Akkermansia</i> were associated with increased tumour burden	colon	C57BL/6 mice	N/A	[244]
Proteobacteria, <i>Desulfovibrio</i> , <i>Erysipelotrichacea</i> , and <i>Fusobacterium</i>	already existing gut microbiota in the rats	natural	higher abundance of Proteobacteria, <i>Desulfovibrio</i> , <i>Erysipelotrichacea</i> , and <i>Fusobacterium</i> in rats with colorectal cancer	colorectal	Wistar rats	“rodent diet”	[136]

Lactobacilli bacteria are protective against cancer in many species

Certain microbes have cancer-preventing effects in both humans and nonhumans.

Lactobacillus is a microbe that is beneficial to many host species, as it protects from colorectal cancer in humans [64, 80–82], 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 [64, 81, 82].

Some microbes have cancer-promoting effects across species

Papillomaviruses have cancer-promoting effects in humans and dogs

Papillomaviruses have cancer-inducing effects in both humans [103] and dogs (Table 1). They induce skin or mucosal malignancies by integrating their genome into the host cells [144], and then their proteins dysregulate pathways of host cell division and DNA damage/stress response [145].

Bacteroides fragilis and *Fusobacterium nucleatum* have cancer-promoting effects in humans and mice

Bacteroides fragilis and *Fusobacterium nucleatum* have cancer-inducing effects in both humans [75, 90–92, 100] and mice (Table 1). *B. fragilis* induce malignancies by producing reactive oxygen species and toxins that damage the host DNA and degrade the cell-to-cell adhesion protein E-cadherin, respectively [146–148]. *F. nucleatum* induce tumourigenesis by entering host cells, promoting their own and the host cells' proliferation,

as well as producing toxins that alter the adhesion and epigenetics of host cells [32, 133, 148–150].

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 [122, 126, 130, 151]. For example, *B. fragilis* has harmful [146, 152] or beneficial effects [153] on the host depending on the diet of the host. The cancer-protective effects of *B. fragilis* may be due to soluble fibers in the host's diet that have anti-inflammatory properties [154].

In other experiments, *Clostridium* species promote gastrointestinal neoplasia in INS-GAS mice on a FVB/N background [155], inhibit proliferation of colorectal cancer cells in C57BL/6 mice [156] and inhibit melanoma in germ-free C57BL/6 mice [139]. *Bacteroides* species promote gastrointestinal neoplasia in INS-GAS mice on a FVB/N background [155], but inhibit melanoma in germ-free C57BL/6 mice [139] (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 [139]; diets not reported in the studies [155, 156]), sex, and age.

Discussion

The idea that food affects health is an ancient idea. This was stated by Hipocrates in ancient Greece “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 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].

Overall in this review we have identified microbial species that have a cancer-promoting and/or cancer-inhibiting effect across several hosts (Table 1). Some microbes show a consistent cancer-promoting or cancer-inhibiting effect across host species, however other microbes do not show a consistent effect. 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 Carnivora have 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 [121]. 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 [101] and mice (Table 1), and are most abundant in carnivorous species [122, 124]. . 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 [40, 165–167].

Litter size might affect cancer susceptibility via the microbiome

The cancer-protective effect of individual *Lactobacilli* species (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 characterized 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 could potentially be one of the reasons 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 [94, 97, 171], as well as carcinogenesis in mice [141], tumour growth in gerbils [142], and overall dysplasia in cats [143] (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 [32, 173, 174]. CagA toxins rewire the host cells' gene expression, induce inflammation, oxidative stress, and alter host cell polarity, which are associated with a high risk of developing gastric and colorectal cancers [94, 173, 174].

The fact that *Helicobacter* bacteria induce cancers in mice, gerbils, cats (Table 1), and humans [97, 171] suggests that *Helicobacter* may be a transmissible agent that causes 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 idea.

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 [19], by sex [20, 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 [139, 146, 152, 153, 155, 156]. 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*, enterotoxigenic *Bacteroides fragilis*, *E. faecalis*, *Peptostreptococcus anaerobius*, *Helicobacter pylori*, and human papillomaviruses [103, 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* produce hydrogen sulfide which can lead to DNA damage [183, 184] *Fusobacterium nucleatum* promotes the expression of mucin and the proinflammatory cytokine tumour necrosis factor alpha [185] tumorigenesis by entering host cells, altering their proliferation and attachment to neighbouring cells [32, 133, 148–150]. 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 [103, 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 [60], and 5000 microbial genomes

across approximately 180 wild and captive species [121], 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 [121, 190], and ninety-nine percent of species in the gut microbiome still cannot be cultured [64]. There are trillions of microbes that are yet to be observed [55].

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 [24, 195–200]. Environments with scarce amounts of plants and high abundance of animal prey favour the evolution of carnivory relative to 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. 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 cancer-promoting 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] may created favourable niches for cancer-inhibiting microbes.

Microbiome and diet interventions could reduce the burden of cancer across species

By utilizing 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 (Figure 1) [213]. Both of these

diets encourage the growth of *Lactobacillus* species [64, 65, 80–82]. Therefore, the cancer-preventing effect of *Lactobacilli* across host species may be tightly linked with and 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.

Dietary interventions could provide cancer protection

Another potential intervention is to manipulate the gut microbiota through altering diet [186], to increase the abundance of beneficial microbes and reduce the abundance of oncogenic microbes in the gut [64, 162, 217]. This has been applied in multiple studies to create an experimentally-induced microbiome suited to study how microbes affect cancer progression. For example, carnivorous and omnivorous animals could periodically be fed a fibrous diet and/or Mediterranean diet. These diets increase the relative abundance of *Bifidobacterium* and *Lactobacillus* spp. [64, 82, 165], which have anti-tumourigenic properties, such as inhibiting cell proliferation and apoptosis, and inactivating carcinogens [82].

More research is needed in order to design these interventions so that they have the intended effects. For example, if we are to modify the diets of zoo animals, we must take into account other adaptations that might help compensate for the increased risk of cancer that is associated with certain diets. Carnivora have a higher malignancy or tumour prevalence than other primarily herbivorous mammalian orders [3, 139], so they might be a species to target for interventions, but it would not be reasonable to assume that a plant-based diet would decrease cancer risk because they have evolved to consume a meat-based diet. Clearly, this is an area where further research is needed.

Probiotic interventions could provide cancer protection

Another intervention option is administering probiotics to prevent or treat cancer [64, 164]. Probiotics are microbes present in certain diets with beneficial effects on the host [218]. Fecal microbiome transplantation has been in use in cancer treatment since the 4th century [219]. Probiotics, such as *Lactobacillus* in yoghurt or administered via fecal microbiome transplantation [220–223], can increase the proportion of beneficial gut bacteria and decrease inflammation in the gut [224, 225].

Probiotics are already standard in the treatment of some cancers. *Mycobacterium bovis* bacillus Calmette-Guerin (BCG) is used in the treatment of non-muscle invasive bladder cancers in humans [214], and have also been used to treat colorectal cancers [226], cervical cancers [227], hepatocellular carcinomas [228], lung cancers [229], as well as melanomas [230]. These microbes appear to stimulate an immune response to the cancers [231, 232]. *In vitro* studies have shown that BCG-activated killer cells can lyse bladder tumour cells. Furthermore, *in vivo* studies have shown that the treatment of bladder cancer is only effective when BCG is administered to immunocompetent C57BL/6 mice, but not NK-deficient mice, showing that natural killer cells play a critical role [232].

More personalised approaches would be ideal for dealing with inter-individual variations in the gut microbiome [162, 163, 233, 234] and administering more effective treatments for specific cancers across the tree of life. For example, different microbial cocktails could be administered to prevent cancers in different species or individuals of the same species with different starting microbiomes.

For example, based on the results in Table 1, *Prevotella*, *Lactobacillus*, *Treponema*, *Roseburia*, *Eubacterium*, and *Ruminococcus* could be administered to prevent and treat colon cancers in Wistar rats, whereas *Lactobacillus rhamnosus* strain GG could be administered to prevent and treat colon cancers in Sprague Dawley rats. *Clostridium butyricum* and *Bacillus*

subtilis could be administered for the prevention and treatment of colon cancers in C57BL/6 mice. These microbes could even be genetically modified via CRISPR/Cas9 technology, to produce microbial strains that overexpress antioxidants or anti-inflammatory proteins [235]. These microbial strains can also be administered in combination with existing chemotherapies, immunotherapies, and adaptive therapies [217, 236]. If the effects on rodents generalise to other species, veterinarians may be able to use these microbes to prevent cancer across species and help in conservation efforts. As the links between diet, microbiome and cancer come to be better understood, it should even be possible to personalise interventions for individuals in the same species that have different diets, microbiomes or immune characteristics.

Prebiotic interventions could provide cancer protection

Prebiotics could also be administered orally for cancer prevention [164]. Prebiotics are nondigestible foods that induce the growth and/or activity of beneficial gut microbiota [215]. Prebiotics or bacterial extracts have been used as a treatment strategy for more than 100 years [214–216]. Prebiotics, such as fructans, galactans, and oligosaccharides including butyrate [164, 237], increase the proportion of beneficial gut bacteria and have anti-inflammatory and anti-cancer properties [224, 225, 238–240].

Microbes can act as biomarkers of cancer

Another important application of this work is in diagnosing cancers earlier through the development of effective non-invasive microbial biomarkers, such as *F. nucleatum* for the detection of colorectal cancers [89, 163]. There may be specific microbes that are associated with different stages of cancer progression and/or microbes that could indicate the effectiveness of different potential cancer therapies.

The protective role of *Lactobacillus* on colorectal cancer in humans [64, 80–82], and lung, colon, and bladder cancers in mice and rats (Table 1), suggests that the prevalence of *Lactobacillus* could be used as a biomarker for lower cancer risk. Already, a lower abundance of *Lactobacillus iners* has been noted in patients with prostate cancer in comparison to healthy people [241]. Whereas, for example, a higher relative abundance of *Helicobacter* bacteria is associated with the development of antrum dysplasia in cats [143], tumour growth in gerbils' intestines [142], gastrointestinal cancers in humans [97, 171], and gastric carcinogenesis in mice [141]. This suggests it could have the potential to be developed as a diagnostic fecal biomarker of different stages of gastrointestinal cancer.

Zoos provide an opportunity for future research

Most of the studies summarised in table 1 used 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 [242]. Broadening this range of hosts to hundreds of species is a key step towards untangling the complex phylogenetic relationships between diet, microbes, and cancer across species.

Most studies in Table 1 were 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 involved with 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 fecal microbiomes. These data could then be compared with cancer data from already existing cancer records in the zoos [168, 243] 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 tumorigenesis in humans and other species, and some microbes, such as the milk-associated *Lactobacillus*, consistently inhibit tumorigenesis in humans and other species (Table 1).

Identifying the diet-related onco biome 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, make these goals entirely possible.

Supplementary

Supplementary Table. List of excluded articles and reason for exclusion.

Competing interests

We declare we have no competing interests.

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Authors' contributions

A.A. conceived the idea for this review. S.E.K. and G.M.A designed, structured, gathered 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, and gave their consent to publish.

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