

Bacteria, food, and cancer

Michelle G. Rooks¹ and Wendy S. Garrett^{1,2,3,4}*

Addresses: ¹Departments of Immunology and Infectious Diseases and Genetics and Complex Diseases, Harvard School of Public Health, Boston, MA 02115, USA; ²Departments of Medicine and Medical Oncology, Harvard Medical School, Boston, MA 02115, USA; ³Dana-Farber Cancer Institute, Boston, MA 02115, USA; ⁴The Broad Institute of MIT and Harvard, Cambridge, MA 02142, USA

* Corresponding author: Wendy S. Garrett (wgarrett@hsph.harvard.edu)

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Abstract

Gut microbes are essential components of the human organism—helping us metabolize food into energy, produce micronutrients, and shape our immune systems. Having a particular pattern of gut microbes is also increasingly being linked to medical conditions including obesity, inflammatory bowel disease, and diabetes. Recent studies now indicate that our resident intestinal bacteria may also play a critical role in determining one's risk of developing cancer, ranging from protection against cancer to promoting its initiation and progression. Gut bacteria are greatly influenced by diet and in this review we explore evidence that they may be the missing piece that explains how dietary intake influences cancer risk, and discuss possible prevention and treatment strategies.

Introduction and context

Like many great political alliances, symbiotic relationships in biology may have started with antagonism, even parasitism, before two parties reached mutual understanding—at least according to some evolutionary biologists. The example that is most often quoted is the mitochondria, the eukaryotic cell's energy-supplying organelle, which may have first graced this planet as a prokaryotic cell. As the story goes, this prokaryote infected a second cell and eventually formed such a close symbiotic relationship that one could not live without the other. This mutual dependence, however, formed over many millennia.

Our own symbionts, the microbes that reside throughout our bodies, and primarily in our guts, have a more independent—some might say rocky—relationship with us, their hosts.

Although these bacteria have long been called commensal (in which only one party derives benefit, but neither is harmed), it is clear that we draw many benefits from their colonization, some of them essential to our health. However, our relationship with gut bacteria is complicated. While gut microbes are essential—helping us metabolize food into energy, produce micronutrients, and shape our immune systems—they are also increasingly being linked to medical conditions including obesity, inflammatory bowel disease, and diabetes. Their influence is not restricted to the effects related to gastrointestinal processes: these symbiotic bacteria may play a critical role across the continuum of cancer, from protection against cancer to promoting its initiation and progression.

One often-cited example of the dangerous side of our gut bacteria is *Helicobacter pylori*, the bacteria responsible for many stomach ulcers, as well as some cancers. Gastric MALT (mucosa-associated lymphoid tissue) lymphoma, a cancer that occurs in the stomach, is frequently associated with *H. pylori*. Not surprisingly then, antibiotics that kill this bacterium cure upwards of 80% of these patients. This infection is also an important risk factor for gastric cancer, which is much more difficult to treat as antibiotics provide no cure. However, harboring this bacterium does not automatically lead to cancer: the guts of almost two-thirds of the world's population are home to *H. pylori*, yet cancer occurs in only a fraction of individuals.

Another example is a toxin-producing Bacteroides fragilis strain that initiates colon cancer in mice and may also do so in humans [1]. This bacterial toxin is a metalloprotease that can drive cleavage of E-cadherin, which then leads to activation of the β-catenin/Wnt pathway, an overactive pathway in almost all colon cancers. In addition, exposure to the toxin activates a transcription factor, nuclear factor kappa-B (NF-κB), which plays important roles in initiation and promotion of epithelial tumorigenesis and is best known as a master regulator of inflammatory response pathways. This strain also drives inflammation, which creates additional conditions that promote cancer formation and progression. Much of the current thinking about how bacteria may contribute to cancers, particularly those of the gastrointestinal tract, involves inflammation.

While many species of bacteria can activate inflammation, it is when bacteria initiate chronic inflammation that cancer risk increases significantly. Inflammatory mediators, like reactive oxygen and nitrogen species, are part of our defense against bacterial pathogens. Persistent exposure to these mediators directly damages host DNA and contributes to genomic instability—a common feature of cancer cells. Certain cytokines and chemokines produced by immune cells function as growth factors or promoters of angiogenesis. NF-κB and STATs (signal transducers and activators of transcription), STAT3 in particular, are transcription factors vital to physiologic inflammatory responses, and are key molecular links connecting inflammation to cancer [2,3].

The innate arm of the immune system's microbial sensors, which recognize patterns shared across many microbes, have recently been shown to intersect with tumor growth pathways. Several studies in mouse models suggest that Toll-like receptors (a major family of receptors that bind these microbe-associated patterns) and their adaptor proteins, such as MyD88, can promote tumorigenesis by affecting both tumor number and size. A seminal paper authored by Seth Rakoff-Nahoum and Ruslan Medzhitov in 2007 [4] showed that tumor development, driven by a heterozygous mutation in the adenomatous polyposis coli gene in mice, was profoundly influenced by MyD88-dependent signaling.

Additionally, the laboratory of Maria Abreu found that deficiencies in Toll-like receptor-4 could prevent colon cancers that usually arise in the setting of chronic inflammation [5]. When overexpressed, this receptor was associated with an increased susceptibility to colon cancer in mice [6]. Patients with colitis-associated cancer also had elevated Toll-like receptor-4 levels, raising the possibility of a novel therapeutic target.

A recent study provides additional insight into MyD88's roles in cancer. MyD88 signaling can alter the stability of c-Myc, an oncoprotein, and activate the epidermal growth factor receptor pathway [7]—two elements often dysregulated in colon cancer. Collectively, these findings suggest that host-signaling pathways that evolved to sense the microbiota can influence cancer development and growth.

But there are other ways that bacteria might contribute to cancer. One of the first recognized beneficial effects on human health was the role our gut bacteria played in digestion and metabolism. Indeed, a look at these bacterial functions is revealing alternate mechanisms by which our gut bacteria both hinder and promote cancer development.

Eating for two

Successful adaptation to the ever-changing human diet is central to the survival of gut microbes. The laboratory of Jeffrey Gordon at Washington University of St. Louis is answering key questions about how diet influences gut bacteria and what has made certain bacteria such successful symbionts. Several other laboratories such as Andy Goodman's at Yale, Ruth Ley's at Cornell, Justin Sonnenburg's at Stanford, and Peter Turnbaugh's at Harvard are now actively investigating the genetic features that make bacteria successful, and what allows them to rapidly respond to dietary changes. The 'Western diet,' a dietary pattern high in fats and simple sugars, can reshape gut microbial ecology and predispose both mice and humans to obesity—a risk factor for certain cancers. Changing from a Western diet to a more prudent (plant-polysaccharide rich) low-fat diet reduces weight and shrinks fat stores in humans and mice, and causes marked shifts in gut microbiota. Researchers observed that after these dietary changes had been adopted long enough to reduce the weight of human subjects and mice, the bacterial profiles of their gut microbiota looked more similar to those of lean control subjects. These experiments provided functional evidence that the gut microbiota may impact energy metabolism and the propensity for obesity [8-10].

Gut bacteria do much to supplement our metabolism. The indigestible leftovers of our diet serve as the major food source for these resident bacteria, the greatest numbers of which reside in the distal gut or the large intestine. They metabolize many dietary fibers that escape host digestion, generating short-chain fatty acids such as acetic, propionic, and butyric acids, which supply an estimated 10% of our daily energy supply [11]. The amount and variety produced are determined by the types of food ingested, how long the food stays in

the gut, and by the bacterial species present in the gut. While humans have the capacity to generate some short-chain fatty acids, the vast majority are produced by the gut microbiota. However, these metabolites do more than provide us with extra energy.

Approximately 95% of gut short-chain fatty acids are absorbed and metabolized by the host for a wide range of physiological functions. Microbial-generated acetate has been shown to bind a G-protein-coupled receptor, GPR43, expressed on immune cells. Deletion of this receptor in mice exacerbated arthritis, asthma, and colitis suggesting that the microbiota's production of acetate may help guide the resolution of inflammatory responses [12]. Acetate also appears to protect the host against infection from pathogenic bacteria, like the intestinal hemorrhage-causing Escherichia coli 0157, by strengthening epithelial barrier function [13]. Propionic acid may also play a role in modulating T helper cell immune responses. However, published observations on butyrate's effects on cell proliferation and apoptosis appear contradictory, making it difficult to interpret its role in cancer prevention and promotion. Butyrate's role as an important energy source for certain epithelial cells types is well established, as is its inhibition of histone deacetylase enzymes. Exposure to butyrate favors histone acetylation allowing DNA within chromatin to become more accessible for transcription-factor binding. Some of butyrate's anticancer effects may involve its ability to change microRNA expression. A recent study by the laboratory of Eugene Chang at the University of Chicago suggests that butyrate slowed the proliferation of a cancer cell line by altering microR106b levels [14]. This family of microRNAs plays important roles in regulating cell cycle progression and is often overexpressed in cancers.

While the mechanistic details of these relationships still need ironing out, such findings, including those from Jeffrey Gordon's group, have ignited the field and are encouraging investigators to look more closely at diet and its influence on gut bacteria, and how these two factors together can influence predisposition to cancer. Support for studying these connections is gaining momentum, and there are an increasing number of funding opportunities and conferences sponsored by the National Institutes of Health (NIH) and private foundations.

From food to cancer

Health experts often tout one type of food or another for their cancer-preventing or cancer-causing properties. While certain foods can increase or decrease a person's chances of developing cancer, researchers are beginning to realize that we can't think of the food we ingest without thinking of the gut bacteria that also ingest our food. One often-cited example is the polyphenol family of chemicals, predominantly found in coffee, tea, wine, fruit, and vegetables, which have been implicated in reducing the risk of cancer. The three main classes of dietary polyphenols include flavonoids, phenolic acids, and lignans. Escaping digestion and absorption in the upper gastrointestinal tract of the host, polyphenols are most readily metabolized in the colon by microbial enzymes. While several members of the *Bacteroides* genus have been shown to metabolize polyphenols, determining the members and role of colonic microbial community in the metabolism of polyphenols is an evolving field that will require both metabolomic and metagenomic approaches, as well as carefully crafted animal studies and human trials [15]. Investigations headed by Tom van de Wiele's group in the Laboratory of Microbial Ecology and Technology at Ghent University have shown that polyphenol consumption in healthy human subjects results in distinct metabolic profiles that are unique to each individual and their microbiota [16]. The metabolism of polyphenols changes their bioavailability; therefore, the variability of health benefits observed in epidemiological studies may be attributable to the composition and relative abundance of the gut microbiota. In addition, our food isn't our only source of polyphenols: clinical studies have shown that when human subjects are given a measured quantity of polyphenols, more polyphenols are produced than consumed [17].

A number of polyphenols, produced by microbes or ingested directly, have anticancer properties. Ellagic acid found in berries and nuts—is one of many plant polyphenol compounds thought to have anti-inflammatory and anticancer benefits. Our gut microbiota are essential for metabolizing ellagic acid into urolithins—compounds believed to be responsible for reducing inflammation and thereby protecting against cancer. The laboratory of Juan Carlos Espín De Gea at the Spanish National Research Council has investigated the anti-inflammatory effects of urolithins in chocolate. In cell culture, urolithin-A was found to down-regulate mRNA expression and protein levels of cyclooxygenase-2—a prostaglandin synthase and a key inflammatory mediator that is inhibited by aspirin and other nonsteroidal anti-inflammatory drugs [18]. They also showed that urolithin-A inhibited the activation of transcription factors like NF-κB and signaling pathways that drive inflammation [19]. Investigators from this lab have also observed similar results in vivo with a rodent model of intestinal inflammation.

Although it is known that a substantial portion of polyphenol metabolites are generated by bacteria in the gut, just how microbiota interact with polyphenols is still not fully understood. In some cases, polyphenols are toxic to microbes. Numerous flavonoid compounds have been able to kill both Gram-positive and Gramnegative organisms in vitro [20]; however, it is not known how dietary phenols may alter microbial composition.

In other cases, polyphenols such as the isoflavones produced by soy and other plants act as antioxidants that mitigate oxidative stress, which is often linked to cancer. Just how soy may modify cancer risk is far from clear. Like other antioxidants, isoflavones are thought to reduce inflammation that predisposes tissues to cancer. The soy isoflavone daidzein is metabolized by certain gut microbes into equol, a plant estrogen. Because of their hormone-like properties, soy isoflavones have been found to have protective effects against prostate cancer; however, these findings are not always consistent across studies [21]. One reason for these inconsistencies could be individual differences in how gut microbes metabolize isoflavones. According to epidemiological studies, only 30-50% of the human population is capable of producing equol. Studies of populations that consume a high level of soy, mostly of Asian descent, have found that equal producers may have a greater reduction in cancer risk than those who do not produce equol [22]. Generally, interpretation of the soy-cancer prevention literature is challenging due to differences in study protocols for monitoring soy intake and measuring the secretion of soy metabolites, and also differences in stratification of subjects based on metabolic profiles. In the future, pairing studies that examine long-term health outcomes with microbial metagenomic analyses that include food frequency data from diverse populations around the world may help to resolve some of the outstanding questions about soy and cancer risk. Although more research is needed to understand the role of our gut microbiota in mediating cancer risk, metabolites such as urolithins, polyphenols, and equol show promise against cancer.

We are studying the effects of dietary interventions such as fermented dairy products and risk-associated foods such as red meat on the microbiota and colon cancer. Our group uses mouse models to control many genetic and environmental factors that complicate human studies of the microbiota and diet. In addition, we make use of mice where we can design the microbial communities from scratch by first generating and breeding mice without any bacteria and then adding back the select bacteria we choose. These so-called germ-free mice can also be transplanted with human fecal samples, which can to some extent 'humanize' these mice.

An incomplete symbiosis

Our gut microbiota, when fed certain foods, can also produce detrimental metabolites that promote cellular proliferation and inhibit apoptosis—auspicious circumstances for cancer development. Heterocyclic amines (HCAs)—the char that graces any well-done steak—are considered procarcinogenic. These compounds resist digestion in the small intestine but remain available for fermentation by bacteria in the colon. Once metabolized by gut bacteria, HCAs are converted to electrophilic derivatives that damage DNA, placing people at increased risk for colon cancer [23].

Hydrogen sulfide is another metabolite produced by gut bacteria that can damage DNA. Consumption of highprotein foods, particularly red meat, may fuel hydrogen sulfide production by sulfur-reducing gut microbes. Some studies suggest that patients with colon cancer and inflammatory bowel disease may harbor higher levels of sulfur-producing bacteria. Studies by Rex Gaskins's lab at University of Illinois at Urbana-Champaign, which investigates the role of sulfate-reducing bacteria in cancer, suggest that hydrogen sulfide can contribute to cancer progression when DNA repair mechanisms are impaired [24]. Whether a greater abundance of sulfur-producing bacteria precedes, or is a result of, these health conditions, and what host factors contribute, requires further investigation. In high-risk individuals, these metabolites may offer targets for cancer prevention.

While we wait for interest from drug companies to develop these targets, some admittedly low-tech solutions have presented themselves. Although not performed frequently, fecal transplants have been used for many decades, though mostly to treat *Clostridium difficile*-associated severe diarrhea and colitis. Increasing antibiotic resistance has renewed interest in alternative bacteriotherapy [25] and its success is raising interest in its use for other ailments.

"It takes a village": the power of community

Although the link between gut microbes and cancer risk will gain prominence, it will probably be years before dropping off a fecal sample at the doctor's office will generate a report of your cancer risk or foods you should or shouldn't eat to modify that risk. Further experimentation is needed to understand the genomic potential and function of the human microbiota. Some of the current bottlenecks are in data processing and analysis.

Indeed, because discoveries of single bacterial species leading to cancer have proven to be the exception, not the rule, the focus is shifting from single organism studies to bacterial communities as a factor influencing cancer risk. Worldwide consortia such as the Human Microbiome Project [26,27] and the Metagenomics of the Human Intestinal Tract project (MetaHIT) [28-30] are applying sequencing-based approaches to study the microbiota of healthy and disease-affected individuals. The emerging field of microbial "omics", which encompasses metagenomics (the total collection of genomes from a microbial community) and metabonomics (the global changes in genes, proteins, and metabolites in a living system [31]), is rapidly advancing. With the decreasing cost of generating microbial metagenomic data and evolving computational tools to analyze it, more investigators will have an enhanced ability to ask new questions about gut bacteria.

Cancer genomics has offered the potential to understand how cancers operate at the molecular level. Microbial metagenomics may have the potential to improve many aspects of cancer prevention and treatment as well. Current studies like the esophageal cancer microbiome project, a joint venture spearheaded by Karen Nelson from the J. Craig Venter Institute and New York University's Zhiheng Pei, aim to identify microbiota-based biomarkers that can identify patients at high risk for developing cancer. Successful biomarker identification will spark interest in the microbiota as a prognostic, diagnostic, and management tool, allowing gut microbiota testing to become part of the evolving personalized medicine tool kit.

In cancer care, cancer genomics and pharmacogenomics are increasingly employed to identify which patients will respond to what treatments and whether particular patients are at risk for developing dangerous drug toxicities. Enzymes produced by gut microbes can often interact with drugs and contribute to side effects or change how the drug is metabolized by the body. A recent study showed that gut bacterial enzymes called β -glucuronidases can contribute to the severe diarrhea that is sometimes associated with a commonly used colon cancer chemotherapy drug called irinotecan [32]. Selectively targeting these bacterial enzymes reduced a potentially life-threatening side effect of this drug.

The day may not be so far off when fecal samples are biobanked for future transplant or high-risk cancer microbiota may be transplanted with lower-risk microbiota. Foods or bacterial-directed therapies may be used to re-engineer gut microbial communities with functions that reduce cancer risk. As we come to understand what features constitute a healthy microbiota and how the microbiota changes across the human lifecycle, the plasticity and genomic potential of our gut microbes may be realized as a fountain of youth and health. As far as

symbiotic relationships go, ours appears to be continually evolving, and Western dietary patterns may be pushing us into a tumultuous relationship. A deeper understanding of the effects of dietary intake on our microbiota will hopefully lead us toward a more perfect union.

Abbreviations

HCA, heterocyclic amine; NF-κB, nuclear factor kappa-B; STAT, signal transducer and activator of transcription.

Competing interests

The authors declare that they have no competing interests.

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