Evidence is emerging that the intestinal microbiota is intrinsically linked with overall health, including cancer risk. Moreover, its composition is not fixed, but can be influenced by several dietary components. Dietary modifiers, including the consumption of live bacteria (probiotics), nondigestible or limited digestible food constituents such as oligosaccharides (prebiotics) and polyphenols, or both (synbiotics), are recognized modifiers of the numbers and types of microbes and have been reported to reduce colon cancer risk experimentally. Microorganisms also have the ability to generate bioactive compounds from food components. Examples include equol from isoflavones, enterodiol and enterolactone from lignans, and urolithins from ellagic acid, which have also been demonstrated to retard experimentally induced cancers. The gastrointestinal microbiota can also influence both sides of the energy balance equation; namely, as a factor influencing energy utilization from the diet and as a factor that influences host genes that regulate energy expenditure and storage. Because of the link between obesity and cancer incidence and mortality, this complex relationship deserves greater attention. Thus, a complex interrelationship exists between the intestinal microbiota and colon cancer risk which can be modified by dietary components and eating behaviors.

Keywords
prebiotics; probiotics; microbiota; colon cancer

Microbes and Colon Cancer

The adult human gut is estimated to contain 100 trillion microbial organisms, collectively referred to as the microbiota [1,2]. The human microbiota is known to be dominated by strict anaerobes including Bacteriodes, Eubacterium, Bifidobacterium, Fusobacterium, Peptostreptococcus, and Atopobium [3]. Facultive anaerobes occur in numbers approximately 1000-fold lower and include lactobacilli, enterococci, streptococci and Enterobacteriaceae [4]. More than 500 different bacterial species may be present in the normal commensal microbiota, although the exact number and the variability among individuals remains an area of investigation [5]. Advances in defining the quality, quantity, and physiologic activity of the intestinal microbiota have occurred as a result of the conversion from culture-based techniques to metagenomics, an emerging field in which the power of genomic analysis (the analysis of
the entire DNA in an organism) is applied to entire communities of microbes. A benefit of this approach is elimination of isolating and culturing individual microbial species. One limitation is that stool and mucosal community populations differ [6,7]. Thus, the analysis of the bacteria in the stool probably does not always reflect that in early parts of the gastrointestinal tract.

A complex dynamic relationship between the host and the gastrointestinal bacteria occurs shortly after birth [8]. The microbiota diversifies as a function of age to form an intestinal microbiota that is unique for each individual [8]. Several findings suggest that the microbial cohort remains relatively constant once adulthood is reached; however, the composition of the resident biota may alter as a result of environmental factors such as diet and antibiotic usage [9].

The colonic microflora has been suggested to have a critical role in setting the tone for a healthy bowel including the risk for developing colorectal cancer [10]. Key physiological functions that might be related to cancer risk include control of epithelial cell proliferation and differentiation, production of essential nutrients and/or bioactive food components, prevention of overgrowth of pathogenic organisms, and stimulation of intestinal immunity [11].

Thus, microbes may influence multiple processes associated with a change in cancer risk. This review provides an overview of the interrelationship of this association as influenced by dietary exposures (Figure 1).

**Yin-Yang and Microbes**

The microflora within the large intestine is provided an opportunity to ferment a range of dietary substances that are not completely digested and absorbed in the small intestine. The two main types of anaerobic fermentation that are carried out in the gastrointestinal tract are carbohydrate and proteolytic [12]. A yin-yang occurs since the main end products of carbohydrate metabolism are thought to be positive while those associated with proteins may be negative. Carbohydrate fermentation produces microbially generated short chain fatty acids (butyrate, acetate and propionate) which can be further metabolized by mammalian cells for energy [12]. In contrast, end products of proteolytic fermentation including phenolic compounds, amines, ammonia, N-nitroso compounds and indoles, can be toxic to the host [12].

Specific strains of bacteria have been implicated in the pathogenesis of cancer, including *Streptococcus bovis*, *Bacteriodes*, *Clostridia*, and *Helicobacter pylori* [13–16]. Conversely, some strains of bacteria, including *Lactobacillus acidophilus* and *Bifidobacterium longum*, have been shown to inhibit carcinogen-induced colon tumor development [17,18]. Thus, a balance between “detrimental” and “beneficial” bacteria has implications in setting the stage for cancer. Shifting the proportion of microbes has been reported to influence carcinogen bioactivation and thus cancer risk. It is increasingly apparent that dietary components can significantly modify this balance.

Interactions between microbes and the genetics of cells lining the intestinal mucosa may also dictate the overall response. Thus, animal models should provide an important tool for characterizing the role of bacteria in understanding the diet-cancer paradigm. There are a number of genetically engineered models of intestinal cancer, such as interleukin-10 and *Muc2* knockout mice [19,20], and *TCRB* and *p53* double knockout mice [21], which when exposed to germ-free conditions appear normal, but when intestinal bacterial colonization is promoted, spontaneously develop intestinal inflammation which is followed by tumors. These studies also suggest that bacterial modulation of intestinal inflammation may be one mechanism whereby the gut microflora may contribute to colorectal carcinogenesis.
Diet influences the amount and strains of gastrointestinal microorganisms

A. Prebiotics

A prebiotic is a nondigestible food ingredient whose beneficial effects on the host result from the selective stimulation of growth and/or activity of the gut microbiota, particularly lactobacilli and bifidobacteria [22]. Most of the attention in this area has been aimed at nondigestible oligosaccharides [23]. Common prebiotics include inulin, other oligosaccharides, lactulose and resistant starch [22]. Dietary fiber has also been shown to convey a prebiotic response [22].

Inulin occurs naturally in several foods such as leek, asparagus, chicory, Jerusalem artichoke, garlic, artichoke, onion, wheat, banana, oats and soybeans [23]. However, these may not be biologically significant sources because Manning and Gibson [10] estimate that an individual would need to consume 4–8 g/day of fructooligosaccharide to significantly (about one log10 value) elevate bifidobacteria in the human gut. A functional food approach has been utilized to add inulin to more frequently consumed products, such as cereals, biscuits, infant foods, yogurts, breads and drinks, at concentrations at which a prebiotic effect may occur [23]. There are also a number of dietary supplements which contain fructooligosachharides, primarily inulin, that are commercially available.

In a double-blind, placebo-controlled, cross-over trial, consuming 30 grams isomalt (a mixture of the polyols 1-O-\(\alpha\)-D—glucopyranosyl-D-mannitol and 6-O-\(\alpha\)-D-glucopyranosul-D-sorbitol) per day for 4-weeks led to a 65% increase in the proportion of bifidobacteria and a 47% increase in total bifidobacteria cell counts compared to feeding sucrose [24]. In another study in which 12 volunteers ingested 10 g inulin/day for 16 days in comparison to a control period without any supplement intake, Bifidobacterium adolescentis showed the strongest response, increasing from 0.89 to 3.9% of the total microbiota [25].

B. Probiotics

In contrast to prebiotics, probiotics are provided in processed foods or in dietary supplements as live bacteria. Yogurt is the most common probiotic-carrying food; however, cheese, fermented and unfermented milks, juices, smoothies, cereal, nutrition bars, and infant/toddler formula all are vehicles for probiotic delivery. The main probiotic supplements on the market utilize lactobacilli, streptococci and bifidobacteria, which are normal constituents of the human gastrointestinal microflora. However, studies are also investigating potential probiotic roles of other microbes such as yeast (Saccharomyces boulardii), which are not normally found in the gastrointestinal tract [26,27]. Probiotic microorganisms do not act exclusively in the large intestine by affecting the intestinal flora but also affect other organs, either by modulating immunological parameters, intestinal permeability and bacterial translocation, or by providing bioactive metabolites [28].

A number of studies with a variety of probiotic strains have been conducted to determine the extent to which probiotics colonize the gastrointestinal tract. These studies have been reviewed by Cothesy et al. [29] and reveal that ingested strains do not become established members of the normal microbiota but may persist only during periods of dosing or for relatively short periods afterwards. Undeniably, greater attention is needed about the most beneficial probiotics and their optimal quantity and exposure duration needed for health promotion.

The combination of a probiotic with a prebiotic to support its viability and activity has been termed a synbiotic [30]. Evidence suggests that synbiotics may be efficacious in altering the composition of the microbiota. For example, the synbiotic combination of a specific oligofructose-enriched inulin (SYN1) and Lactobacillus rhamnosus GG and Bifidobacterium lactis Bb12 for 12 weeks caused a 16% and 18% increase in the numbers of Lactobacillus and

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Bifidobacterium, respectively, and a 31% decrease in the numbers of Clostridium perfringens [31]. Recent in vitro studies have demonstrated that synbiotics were more effective than prebiotics or probiotics in modulating the gut microflora [32]. These findings need to be documented in well controlled human intervention studies.

The gut microbiota may mediate the effects of diet as a modifier of colon cancer risk. An increase in the number of bifidobacteria and/or lactobacilli resulting from the use of probiotics, prebiotics or synbiotics has been demonstrated to protect against chemically induced colonic DNA damage in animal models [33]. Interestingly, several strains of lactobacilli and bifidobacteria were effective in protecting rats from this DNA damage, as measured by the Comet assay [34]. Rowland et al [18] reported that in rats inoculated with human flora and fed a diet containing lactulose compared to those fed a diet containing a comparable amount of sucrose that their colonocytes had less DNA damage following oral treatment with dimethylhydrazine [18]. More recently, another plausible mechanism has surfaced in the synbiotic combination of resistant starch, Lactobacillus acidophilus and Bifidobacterium lactis [34]. These investigations identified enhanced apoptosis of carcinogen-damaged cells in rat colon by the combination treatment [34]. In contrast, the probiotics provided no protection when a low resistant starch diet was fed and the resistant starch had no protective response in the absence of the probiotic [35].

In addition to a potential role in the prevention of cancer, probiotics have also been suggested to enhance the immune system and inhibit the growth of existing tumors [36]. For example, probiotics containing lactic acid bacteria increased the survival rate of mice injected with tumor cells which correlated with an increase in cellular immunity as reflected an increase in the number of total T cells, NK cells and MHC class II+ cells, and CD4-CD8+ T cells [37]. Moreover, peptidoglycan from a lactobacillus species produced a dose-dependent reduction in the growth of CT26 colon cancer cells in mice via increased apoptosis but had no effect on apoptosis of these cells in vitro, suggesting that the in vivo anti-tumorigenic effect may have been mediated by an immune response [38].

C. Combined Response

Providing prebiotics, probiotics, or a combination is known to inhibit aberrant crypt foci (ACF), a preneoplastic lesion for colon cancer. For example, rats fed a high-fat and low-fiber diet supplemented daily with the probiotic B. polyfermenticus (3 × 10⁸ cfu/1.3g) had a 50% reduction in ACF formation compared to rats fed the control diet [39]. Similarly, several studies have found that adding a relative large amount of inulin (10%) to a diet reduced ACF [40–42]. Synbiotics may be particularly efficacious for reducing colonic preneoplastic lesions based on studies by Rowland et al. [40]. They found that the combination of inulin and Bifidobacterium longum decreased ACF formation by 80% whereas inulin alone decreased ACF by 41% and Bifidobacterium longum alone decreased ACF by 26%. Studies in experimental animals have also suggested that prebiotics are protective against tumor development. For example, fruco-oligosaccharides reduced the occurrence of colon tumors in Min mice, a genetic model of human colon cancer [43].

Probiotics and synbiotics have also been found to be efficacious against risk factors for colon cancer in humans. A four-year study of 398 subjects found that Lactobacillus casei decreased the recurrence of atypical colonic polyps [44]. A human clinical trial was recently conducted to examine the effect of a synbiotic product containing the probiotic strains Lactobacillus rhamnosus GG and Bifidobacterium lactis Bb12 and the prebiotic inulin or a placebo (maltodextrose) on biomarkers of colon cancer risk in 37 colon cancer patients and 43 polypectomized patients [31,45]. The synbiotic treatment of polyp patients was most effective in reducing DNA damage, colonocyte cell proliferation and fecal water genotoxicity (used as a biomarker for colon cancer risk) [46]. Synbiotic consumption prevented an increased secretion
of interleukin-2 by peripheral blood mononuclear cells and increased the production of interferon in the cancer patients [31]. These results suggest that synbiotics can reduce multiple factors associated with colon cancer risk in humans.

**D. Other Dietary Modifiers**

Several dietary components, other than complex carbohydrates, may modulate the microbiome. When bacteria are cultured with various polyphenols that occur in tea the growth of certain pathogenic bacteria such as *Clostridium perfringens* and *Bacteroides* was significantly repressed, while commensal anaerobes like *Bifidobacterium* and *Lactobacillus* were affected less [46]. Interestingly adding bacterial metabolites of the tea polyphenols was found to lead to a similar response. To date several polyphenols (caffeic acid, catechin, epicatechin, coumaric acid, phloridzin, rutin, naringenin, daidzein, genistein and quercetin) have been demonstrated to inhibit the growth and adhesion of bacterial pathogens to human Caco-2 cells, and to enhance the proliferation and adhesion of a probiotic, *L. rhamnosus* [47]. Providing wine polyphenols (57 mg/kg body weight by gavage for 10 days) resulted in predominantly fecal *Bacteroides*, *Lactobacillus* and *Bifidobacterium* in rats compared to the controls which had predominantly *Bacteroides*, *Clostridium* and *Propionibacterium* [48]. It remains to be determined whether wine consumption or consumption of other polyphenols results in a similar effect in humans.

A host of food constituents have been reported to have bactericidal properties [49]. Among the plants that killed *H. pylori*, turmeric was the most efficient, but ginger, chili, black caraway, oregano and licorice were also bactericidal. It remains unclear if these agents have physiological importance in modulating the number and types of microorganisms in the gastrointestinal tract following traditional exposures.

**Diet can also influence cancer risk by modifying microbial metabolism**

Bacterial transformation of dietary components and other chemicals in the intestinal lumen are associated with the production of carcinogenic agents and may therefore be another mechanism whereby the gut microflora may influence cancer risk. Microbial enzymes including nitroreductases, azoreductases, hydrolases and β-glucuronidase, can convert inactive compounds to active metabolites which may exert adverse effects. For example, β-glucuronidase hydrolyzes glucuronic acid conjugates of heterocyclic amines (carcinogens formed in food during cooking), to form reactive metabolites which can damage the colonic mucosal cells [50].

Evidence has revealed the potential of probiotics, prebiotics and synbiotics to reduce toxic metabolite production in the gut. In a study using a synbiotic mix of *Bifidobacterium longum* and dietary inulin (5% w/w), human fecal associated rats fed the active diets had 55% lower fecal β-glucoronidase activity and 30% lower ammonia concentrations than the control rats [37]. Furthermore, the synbiotic mix was more efficacious than either probiotic or prebiotic alone [37]. Mice fed yogurt had reduced β-glucoronidase and nitroreductase activities [51]. Similarly, in 36 humans fed lactulose twice daily (2 × 10 g/day) for 4 weeks, there was a significant reduction in fecal azoreductase, 7α-dehydroxylase, β-glucuronidase, nitroreductase and urease activities, as well as a reduction in fecal concentrations of cresol, indole, phenol and skatol compared to when they were fed a placebo [52].

Some polyphenol containing dietary components may also influence bacterial metabolizing enzymes and thus influence overall cancer risk. For example, resveratrol supplementation (8 mg/kg body weight/day, intragastrically) significantly reduced activities of fecal and host colonic mucosal enzymes, such as β-glucoronidase, β-glucosidase, β-galactosidase, mucinase, and nitroreductase activities (21%, 45%, 37%, 41% and 26% respectively) compared to control...
animals [53]. The reduced bacterial enzyme activity was associated with a significant reduction in colonic tumor incidence in the resveratrol fed compared to control rats [53].

The mechanism(s) accounting for these food related alteration in bacterial and host enzymes are not currently known. While these observations are intriguing, it remains to be determined if these changes are a result of modifications of enzymatic activity within a subpopulation of microorganisms or a change in the proportion of specific bacteria. Regardless, they are another mechanism whereby dietary components can interact with the microbiota to influence colon cancer risk.

**Bacteria can influence cancer risk by modifying metabolism of dietary components**

Bacteria may also generate new metabolites, which are more biologically active, from dietary components (Table 1). For example, short chain fatty acids, which are formed from the bacterial fermentation of indigestible carbohydrates, are nutrients and growth signals for the intestinal epithelium and may play a role in colon cancer prevention [5]. Butyrate is the most widely studied of these short chain fatty acids and the preferred energy source of colonocytes. In normal colonocytes, butyrate prevents apoptosis and subsequent mucosal atrophy [54,55]. In contrast, in colon carcinoma cells, butyrate has been shown to stimulate differentiation, inhibit cell proliferation, induce apoptosis and inhibit angiogenesis [56–58]. Additionally, butyrate protects human colon cells from DNA damage [59]. At a molecular level, butyrate has been shown to affect gene expression via the phosphorylation and acetylation of histone proteins, particularly H3 and H4 [60]. Hyperacetylation of histones disrupts ionic interactions with the adjacent DNA backbone, creating less densely packed chromatin, or euchromatin, and allows transcription factors to activate specific genes.

Human and animal studies of butyrate production and cancer risk are difficult to perform. This difficulty stems from dietary butyrate being fully absorbed in the small intestine; whereas colonic butyrate is endogenously produced by bacterial fermentation of luminal carbohydrates [61,62]. Nevertheless, animal studies have shown that the production of short chain fatty acids correlates with bacterial modulation of colonocyte proliferation, differentiation and apoptosis [61]. Furthermore, luminal delivery of butyrate at high concentrations appears to reduce aberrant crypt formation by 45% compared to untreated rats [62]. In humans, the relationship between luminal butyrate exposure and colorectal cancer risk has only been examined indirectly in case-control studies, by measuring fecal butyrate concentrations. Unfortunately this may not accurately reflect colonic butyrate exposure [63]. Future studies are needed which focus on understanding how different types of dietary fiber influence colonic butyrate production, the influence of age and stage of the cancer process as a variables, and better ways to assess luminal butyrate exposure.

In addition to butyrate, bacteria are also involved in the formation of another group of beneficial fatty acids; namely conjugated linoleic acids (CLA). These are a group of isomers of linoleic acid possessing anti-inflammatory and cancer protective properties [64]. Several studies have investigated the conversion of linoleic acid to CLA when incubated with various strains of lactobacilli and bifidobacteria [65,66]. A combination of probiotic bacteria has been shown to convert linoleic acid to CLA, decreasing cancer cell viability and inducing apoptosis [64]. One isomer, 9t,11t-CLA, inhibits the development of carcinogen-induced ACF in rat [67] and polyp number in Min mice [68].

One of the most abundant isoflavones in soy, daidzein, is differentially metabolized to equol and O-desmethylangolensin (DMA) by gut microflora in humans [69]. Recent investigations suggest a consortium of bacteria may be involved in equol production [70], and the bacteria...
responsible for equol production differ from the bacteria responsible for DMA production. Equol and DMA have been detected in a variety of body fluids, including blood, urine, feces, prostatic fluid and breast tissue [71,72]. Equol and DMA have been shown to bind to human estrogen receptors α and β with a greater affinity than the parent compound, daidzein [73,74]. Furthermore, in studies that have assessed estrogen receptor-dependent transcription of β-galactosidase in transfected yeast assays, equol induced transcription to a greater extent than daidzein, in yeast carrying estrogen receptor α or β [75]. Therefore, because equol mediates many of its biological effects by binding to the estrogen receptors, in vitro studies suggest that equol is more biologically active than daidzein.

The capacity to form equol, which is present in approximately 30–40% of humans, is positively correlated with an abundance of sulfate-reducing bacteria and negatively with Clostridium coccoides-Eubacterium rectale counts [76]. Furthermore, individuals with a higher PUFA and alcohol intake were more likely to be strong equol producers [76]. An individual’s ability to produce equol appears to be relatively stable over time. A 2-month intervention with a symbiotic capsule containing a total of 10^9 colony-forming units of Lactobacillus acidophilus and Bifidobacterium longum and 10–15 mg fructooligosaccharides did not significantly alter equol production or plasma hormone concentrations in premenopausal women [77] or in men [78]. Similarly, equol excretion was not altered after soy protein or wheat bran consumption [79, 80]. Data such as this suggests that equol production is quite consistent in most individuals and the primary determinant is the occurrence of selected microbes. Why these exist in some individuals and not in others remains to be resolved.

Besides daidzein, other plant components can be metabolized by intestinal bacteria to cancer protective compounds. For example, plant lignans can be converted to the mammalian lignans, enterodiol and enterolactone by the intestinal microbiota. In contrast to the bacterial production of equol, which only occurs in about one-third of the population, the conversion of secoisolarciresinol to enterodiol and enterolactone occurs in most individuals [81]. Eleven bacterial species involved in the metabolism of secoisolaricresinol diglucoside have been isolated from human feces or obtained from bacterial culture collections [82]. Flaxseed is the richest source of lignan precursors in the typical human diet [83]. However, the total plant lignan concentration in sesame seed (2180 μmol/100 g) was higher than in flaxseed (820 μmol/100 g) [84]. In vitro fermentation with human fecal inoculums demonstrate that sesamin can be converted to lignans suggesting that sesame seed may also be a rich dietary source in humans [84]. Gut microbial metabolites of plant lignans may also have beneficial effects against colon cancer. Elevated plasma concentrations of enterolignans, in particular, enterodiol, were associated with a significant reduction in colorectal adenoma risk in a case control study [85]. Enterolactone has been reported to induce apoptosis and inhibit growth of Colo201 human colon cancer cells in culture and following transplantation into athymic mice [86]. Similarly, SW480 cell growth is inhibited in a dose- and time-dependent manner by enterolactone and enterodiol [87]. Feeding the lignans matairesinol and secoisolaricresinol to Min mice, increased plasma concentrations of enterolactone and enterodiol but did not inhibit intestinal tumorigenesis [88]. In contrast, secoisolaricresinol diglucoside concentrations from wheat bran from four selected wheat cultivars correlated with the cancer protective effects in Min mice, suggesting that secoisolaricresinol diglucoside may contribute to the cancer preventive effects of wheat bran [88]. The reasons for these inconsistencies are unclear but warrant additional examination.

Prenylflavonoids including xanthohumol, isoxanthohumol and 8-prenylnaringenin (8-PN), are found in hops and hop-derived products such as beers [89]. 8-PN is formed by bacterial metabolism of isoxanthohumol and is one of the most potent phytoestrogens [90]. In contrast, 8-PN is less efficacious than xanthohumol in inhibiting growth of colon cancer cell lines [91]. Recently, it was shown that intestinal 8-PN production only occurs in one-third of humans,
and it is clear that substantial interindividual differences exist in the production of this active metabolite, which may be associated with differences in health benefits [90]. Brunelli et al. [92] provided evidence that 8-PN inhibits epidermal growth factor-induced MCF-7 breast cancer cell proliferation by targeting phosphatidylinositol-3-OH kinase activity.

Ellagic acid, a polyphenol which is present in many foods including strawberries, raspberries, walnuts and pomegranates, has been reported to show a multitude of biological properties including antioxidant and cancer protective activities [93]. Ellagic acid is metabolized by human colonic microflora to yield urolithins A and B [94]. These urolithins have been shown to exert both estrogenic and antiestrogenic activities. Both urolithins A and B showed estrogenic activity in a dose-dependent manner even at high concentrations (40 microM), without antiproliferative or toxic effects towards MCF-7 breast cancer cells. They also exhibit antiestrogenic activity by antagonizing the growth promoting effect of estradiol in a dose-dependent manner [94]. Similar to equol, the production of urolithins has been hypothesized to depend on the microflora. Large interindividual variability in production has been reported and the reason remains poorly understood [94]. The bacteria responsible for the production of urolithins remain to be characterized. The variability was demonstrated in a human supplementation study: when 10 volunteers consumed 25 g fresh strawberries, excretion of urolithin B derivatives ranged from 0.05 to 6.3% [95]. When they consumed 35 g of walnuts, the excretion ranged from 1.2 to 81%. Consuming 300 ml of oak-aged red wine caused a range of excretion from 1.8 to 7.4% [95]. The potential biological effects for this cancer protective dietary compound may also be different among individuals depending on their microflora.

Metabolism by gut microflora may also influence tissue exposure to higher-molecular-weight polyphenols including proanthocyanidins or oxidized polymeric polyphenols, which are poorly absorbed in the proximal part of the gastrointestinal tract. These polyphenols are abundant in wine, tea, chocolate and many fruits [96]. A major fraction of the polyphenols present in the plasma and excreted in urine of rats fed red wine polyphenols are aromatic acid metabolites formed in the gut [97]. Incubating an anthocyanin extract from Cabernet Sauvignon grapes with the contents of the large intestine of pigs, after 6 hours results in a loss of the parent compound but the generation of three identifiable metabolites [98]. It is possible that these metabolites offer the protective effect against colon cancer, such as decreased carcinogen-induced aberrant crypt formation, colonic cell proliferation and oxidative DNA damage, which have been attributed to anthocyanin consumption [99]

The dynamic relationship between obesity and the gut microbiota: another link to cancer?

Obesity has been linked with both cancer incidence and mortality [100]. Recent evidence suggests that the gut microbiota affects nutrient acquisition and energy regulation; it further suggests that obese and lean people have a different microbiota [101–105]. Investigators have used genetic sequencing to identify the different strains of bacteria in the gut of 12 obese individuals and compared them with five lean volunteers [103]. Obese individuals had more Firmicutes and nearly 90% less Bacteroidetes than the lean individuals. Furthermore, when obese volunteers consumed a low-fat or low-carbohydrate diet for one year and lost as much as 25% of their body weight, the proportion of Firmicutes in their colon dropped and that of the Bacteroidetes rose. However, the levels of the two types of bacteria never reached those of the group that was lean in the beginning [103].

Differences in fecal microbiota of infants (6 and 12 months) have been associated with the risk of being overweight or obese 7 years of age [106]. Children of normal weight had higher Bifidobacterial and lower Staphylococcus aureus concentrations at ages 6 and 12 months than did children who became overweight/obese [106]. These results suggest that differences in the
microbiota precede overweight/obesity. Future work is needed to determine whether manipulation of the gut microbial community could be an approach for the treatment and/or prevention of obesity.

Conventionally reared mice have a 40% higher body fat content and 47% higher gonadal fat content than germ-free mice even though they consume less food than their germ-free counterparts [101]. Furthermore, when the distal gut microbiota from the normal mice was transplanted into the gnotobiotic mice, there was a 60% increase in body fat within 2 weeks without any increase in food consumption or obvious differences in energy expenditure. These results support the hypothesis that the microbiota affects the amount of energy extracted from the diet. Mechanistic studies revealed that the transplanted microbiota not only increased caloric release from dietary plant polysaccharides with glycosidic linkages that the host is ill-equipped to cleave with its own complement of glycoside hydrolases, but also modulates host genes that affect energy deposition in adipocytes including fasting-induced adipocyte factor (Fiaf) [101]. Fiaf is a circulating lipoprotein lipase inhibitor and its suppression is essential for the microbiota-induced deposition of triglycerides in adipocytes. These findings suggest that the composition of the gut microbial community may affect the amount of dietary energy that is extracted [101].

Similar to humans, mice that are genetically obese (ob/ob) have a higher proportion of intestinal Firmicutes and 50% fewer Bacteroidetes than their lean siblings [102]. When germ-free mice were colonized with either the microbiota from obese (ob/ob) or lean (+/) littermates, the mice given the microbiota from obese mice extracted more calories from their food and had a significantly greater increase in total body fat than in mice colonized with the microbiota from lean mice (mean percent of fat gain, 47% versus 27%; representing a difference of 4 kcal/g or 2% of total calories consumed) [103]. These data suggest that differences in the efficiency of caloric extraction from food may be determined by the microbiota, further suggesting a microbial component in the pathogenesis of obesity.

In contrast to mice with a gut microbiota, germ-free animals are protected against the obesity that develops after consumption of a Western-style, high fat, sugar-rich diet [104]. Their continuously lean phenotype is associated with increased skeletal muscle levels of AMP-activated protein kinase and its downstream targets involved in fatty acid oxidation such as acetyl CoA carboxylase and carnitine-palmitoyl transferase [105]. Moreover, germ-free knockout animals lacking Fiaf are not protected from diet-induced obesity because of reduced expression of genes involved in fatty acid oxidation [105]. These findings suggest that the gut microbiota can influence both sides of the energy balance equation; namely, as a factor that influences energy utilization from the diet and as a factor that affects host genes that regulate how energy is expended and stored [105]. It is not currently known whether the microbiota has a similar effect on energy utilization and gene expression patterns in humans.

Conclusion

A complex interrelationship exists between the intestinal microbiota and colon cancer risk which can be modified by dietary behavior. Not only can eating behaviors modify the numbers and types of microorganisms, but microorganisms can also generate new compounds from food components some of which can be beneficial while others may be harmful. Many of the specific bacteria, as well as microbially generated metabolites, may have a role in cancer risk or development. More in depth studies investigating the interrelationships among intestinal bacteria, diet and cancer risk are desperately needed. Many unanswered issues remain including: a better understanding of how an individual’s genetic background influences their microflora; who might benefit from dietary interventions to alter their indigenous microflora; what are the microbially generated metabolites of bioactive food components; how can these
be utilized to better understand their molecular targets/mechanisms for cancer prevention; and, can we identify inter-individual variability in the production of these metabolites? Once answers to these fundamental questions are available, it should be possible to develop specific dietary recommendations for cancer prevention based on modification of the composition or activities of the colon’s commensal microflora.

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Figure 1.
A dynamic relationship exists among the gastrointestinal microbiota, the intake and metabolism of dietary bioactive food components and energy, and the intestinal mucosal cells. Both the numbers and types of microbes and dietary factors can influence colon cancer risk and tumor behavior. Genomics within the microbes and the mucosal cells can influence the direction and/or magnitude of this relationship.
## Table 1
Bacterial metabolites from dietary components with cancer preventive properties

<table>
<thead>
<tr>
<th>Dietary Component</th>
<th>Food Sources</th>
<th>Bacterial Metabolite</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fiber</td>
<td>Grains/grain products</td>
<td>Butyrate</td>
<td>54–63</td>
</tr>
<tr>
<td>Linoleic acid</td>
<td>Vegetable oils</td>
<td>Conjugated linoleic acid</td>
<td>64–68</td>
</tr>
<tr>
<td>Daidzein</td>
<td>Soy</td>
<td>Equol</td>
<td>69–80</td>
</tr>
<tr>
<td>Secoisolariciresinol</td>
<td>Flaxseed, sesame</td>
<td>Enterolactone, Enterodiol</td>
<td>81–88</td>
</tr>
<tr>
<td>Isoxanthohumol</td>
<td>Hops/hop-derived products such as beer</td>
<td>8-Prenylnaringenin</td>
<td>89–92</td>
</tr>
<tr>
<td>Ellagic acid</td>
<td>Strawberries, raspberries, walnuts, pomegranates</td>
<td>Urolithins A and B</td>
<td>93–95</td>
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</tbody>
</table>