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**Abstract**
Colon cancer is the third most commonly diagnosed type of cancer in the United States. Lifestyle and dietary patterns influence colon cancer risk both positively and negatively. Among the dietary factors, several plant-derived compounds have been found to afford colon cancer protection. These compounds potentially influence all aspects of colonic cellular regulation and develop complex interrelationships with the colonic microbiome. Increasing understanding of the role of microorganisms in determining the colonic environment has led to awareness of this important interrelationship among dietary factors and the microbial population. Plant-derived polyphenols are active mediators of cellular events, target key carcinogenic pathways, and modulate colonic microbial populations. In turn, the colonic microorganisms metabolize dietary compounds and mediate cellular events. In addition, the role of estrogen receptors in colon cancer and the importance of dietary components that mediate estrogen receptor-β are increasingly being discovered. Hence, dietary bioactive compounds and the intestinal microbiota create a complex milieu that directly affects the carcinogenic events of the colon. These relationships must be carefully characterized in future research to provide dietary recommendations that will reduce colon cancer risk.

**Keywords**
diet, colon cancer, polyphenols, estrogen receptor, bioactive components

**Disciplines**
Food Science | Human and Clinical Nutrition | Oncology

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# Influence of Dietary Phytochemicals and Microbiota on Colon Cancer Risk

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**ABSTRACT:** Colon cancer is the third most commonly diagnosed type of cancer in the United States. Lifestyle and dietary patterns influence colon cancer risk both positively and negatively. Among the dietary factors, several plant-derived compounds have been found to afford colon cancer protection. These compounds potentially influence all aspects of colonic cellular regulation and develop complex interrelationships with the colonic microbiome. Increasing understanding of the role of microorganisms in determining the colonic environment has led to awareness of this important interrelationship among dietary factors and the microbial population. Plant-derived polyphenols are active mediators of cellular events, target key carcinogenic pathways, and modulate colonic microbial populations. In turn, the colonic microorganisms metabolize dietary compounds and mediate cellular events. In addition, the role of estrogen receptors in colon cancer and the importance of dietary components that mediate estrogen receptor-$\beta$ are increasingly being discovered. Hence, dietary bioactive compounds and the intestinal microbiota create a complex milieu that directly affects the carcinogenic events of the colon. These relationships must be carefully characterized in future research to provide dietary recommendations that will reduce colon cancer risk.

**KEYWORDS:** *diet, colon cancer, polyphenols, estrogen receptor, bioactive components*

## INTRODUCTION

Colon cancer remains the third most commonly diagnosed type of cancer in the United States, with lung topping the list and either breast in women or prostate in men, second (NCI statistics, www.seer.cancer.gov). For 2010, approximately 142,570 men and women were diagnosed with colon cancer, and about a third will die from the disease, therefore making this an important health problem. The lifetime risk of developing colon cancer is around 5% and the average age at diagnosis is 70. Because of the later age of onset of colon cancer, and the direct interaction of colonic cells with dietary components, cancer of the colon is highly responsive to lifestyle and environmental factors, especially diet.[1] In an extensive review of the epidemiological evidence through 2007, it was concluded that there was probable evidence that foods containing dietary fiber, garlic, milk, and calcium and limited suggestive evidence that nonstarchy vegetables, fish, fruits, and foods containing folate, selenium, or vitamin D were protective against colorectal cancers in humans.[2] Lifestyle factors have been correlated with increasing colon cancer risk, including low physical activity and abdominal fatness. More controversial is the link between intake of red meat and colon cancer. Large meta-analyses have found both increased[3] or no increased[4,5] risk associated with red meat consumption.

The positive link between diet and colon cancer was first recognized over four decades ago when it was observed that consumption of high amounts of fiber by African populations was associated with low incidence of colon cancer.[6] Over the subsequent years, diets high in dietary fiber and whole grains have been consistently linked with reduced colon cancer risk.[7] More recently, protective dietary associations with high frequency of consumption of fruits and vegetables,[8] green tea,[9] and soy[10] have also been linked to reduced colon cancer risk. Because these foods are rich sources of bioactive phytochemicals, there is active research to identify these compounds and describe their function in the colon. A partial list of the most well-studied phytochemicals associated with reducing colon cancer and proposed mechanisms of action for dietary compounds is shown in Table 1.

**Table 1. Potential Food Components and Mechanisms for Reducing Colon Cancer Risk**

| Potential Cancer Protective Dietary Bioactive Compounds | |
|---|---|
| curcumin | Shehzad et al., 2010[54] |
| epigallocatechin gallate | Yang et al., 2011[97] |
| resveratrol | Rimando et al., 2008[46] |
| quercetin | Kyle et al., 2010[52] |
| genistein | Barone et al., 2012[81] |
| sulforaphane | Clarke et al., 2008[98] |
| lignans | Aehle et al., 2011[94] |
| **Potential Anticarcinogenic Mechanisms for Bioactive Compounds** | |
| cell growth arrest | Davis et al., 2010[18] |
| induction of apoptosis | Pan et al., 2011[99] |
| inhibition of COX-2 | Romagnolo et al., 2011[100] |
| regulation of inflammation | Havenaar et al., 2011[43] |
| modification of microbial population | Azcarate-Peril et al., 2011[39] |
| signaling pathway regulation (e.g., Wnt) | Tarapore et al., 2012[16] |
| epigenetic changes | Link et al., 2010[17] |
| estrogen receptor | Gallo et al., 2012[82] |

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## COLON CANCER ETIOLOGY

The etiology of colon cancer has been well studied, and genetic mutations have been identified.[11] Approximately 15−30% of colon cancer occurrence is associated with a hereditary component. Among these, familial adenomatous polyposis (FAP) is rare, but carriers have an almost 100% risk of adenocarcinoma. Hereditary nonpolyposis colorectal cancer (HNPCC) associated with mutation to DNA mismatch repair genes also correlates with high risk of cancer. Despite these known genetic factors, the majority of colon cancer cases are considered to be sporadic and associated with lifestyle or environmental factors.

Specific molecular events associated with the progression of both hereditary and sporadic forms of colon cancer have been reviewed previously;[12] therefore, a full description is beyond the scope of this review. Briefly, among the first changes are in the adenomatous polyposis coli (APC) gene, which result in dysregulation of the Wnt pathway. In the intestine, the Wnt pathway is centrally involved in regulatory aspects of cellular proliferation and organization.[13] The APC protein directly modulates the transcription factor $\beta$-catenin such that when APC is lost or truncated, $\beta$-catenin translocates to the nucleus and up-reglates transcription of Wnt target genes. Experimentally induced stabilization of Wnt signaling correlates with dysplasia, cellular overgrowth, and loss of structure.[13] It has been documented that abnormal cellular proliferation within early cancer lesions, known as aberrant crypt foci (ACF), is associated with Wnt up-regulation.[14] Subsequent mutations within the intestine ultimately lead to aneuploidy, methylation of CpG islands, cyclooxygenase-2 (COX-2) activation, and microsatellite instability. Additionally, tumor growth is promoted by up-regulated angiogenesis associated with dysregulation of the Wnt pathway, vascular endothelial growth factor (VEGF), COX-2, and a wide range of other signaling systems.[15] As a result of the loss of cellular regulation, adenomatous polyps, or adenoma, arise from the epithelium. Adenomas are present in about 25% of people over the age of 50 and 50% of those over age 70. Polypectomy, which can be done during screening colonoscopies, reduces the risk of cancer. On the basis of the known pathways associated with colon cancer etiology, finding dietary components that alter the Wnt/$\beta$-catenin pathway, COX-2, methylation, and microsatellite instability would be the most beneficial for cancer prevention.[16,17] Also, dietary factors that inhibit cell proliferation and angiogenesis and/or induce apoptosis would also be beneficial.[18]

## INFLAMMATORY BOWEL DISEASE AND COLON CANCER

Ullman et al.[19] described the scenario of how inflammation in the colon can lead to cancer. Following an environmental trigger, a host of events ensue, which create an inflammatory situation in the colonic environment. Enhanced production of reactive oxygen and nitrogen species, presumably from the innate and adaptive immune systems, may lead to damage to DNA, RNA, proteins, and lipids. An important mediator in this process may be TNF-$\alpha$, which is released from activated macrophages and T cells and binds to the TNF-receptor. TNF-$\alpha$ has been associated with promotion of DNA damage, inducing angiogenesis, and induction of COX-2.[20] TNF-$\alpha$ activates NF-$\kappa$B, a transcription factor, and NF-$\kappa$B can also be activated by bacteria in the colon, presumably via the Toll-like receptors.[21,22] Activation of NF-$\kappa$B in immune cells leads to increase release of cytokines including IL-6, which, through binding to IL-6-receptors, initiates signaling pathways[19,23] leading to inflammation. The important role of inflammation in colon cancer development has been documented from both human studies and animal models.[24,25]

Recently, the number of Americans who have been diagnosed with inflammatory bowel disease (IBD), which is the umbrella term for colitis and Crohn's disease, has increased significantly.[26,27] Patients with IBD have an elevated risk of colon cancer, which is compounded by the length of time with the disease and its severity.[28] In animal studies, inflamed mucosal cells are more likely to progress to cancer.[29] The mechanisms through which inflammation in the colon progresses to cancer are not fully understood; however, it has been proposed that hypermethylation of tumor suppressors and DNA mismatch repair genes are likely early events.[30] Several years ago it was clearly shown that anti-inflammatory drugs such as aspirin[31] and those that inhibit COX-2[32] were protective against colon cancer in humans. Hence, a major focus of research is to understand these inflammatory pathways and to find dietary components that protect and reduce inflammation.

## COLONIC MICROBIOTA AND COLON CANCER

Notable in the development of colon cancer is the intimate involvement of colonic microbiota. The intestinal tract is the largest source of microorganisms in the body. The entire intestinal tract harbors microorganisms, but the population density occurs along a gradient, with the stomach containing $10^3$; the jejunum, $10^6$; the terminal ileum, $10^9$; and the colon, around $10^{11}$ microorganisms per gram of intestinal content.[33,34] It has been estimated that humans have over 1000 different bacterial species in the gastrointestinal (GI) tract, most of which have never been fully characterized. A phylogenetic analysis of microorganisms from 107 samples of human colon found that the majority of bacterial sequences were associated with the same four phyla of bacteria: Firmicutes, Bacterioidetes, Actinobacteria, and Proteobacteria.[35] This was consistent among patients with IBD and controls. The relative ratios of these bacteria phyla differ between the colon and small intestine. Studies have found differences among patients with and without colorectal cancer in the population of bacteria phyla.[36] Some phyla are increased, whereas others are decreased. Exactly how these changes affect the cancer process, however, is not clear.

The microflora of the colon contributes significantly to the colonic environment. Microorganisms produce, digest, and metabolize colonic compounds, which influences their bioavailability; they compete for nutrients with each other; they communicate with the colonic mucosa to sense changes in the colonic environment and mediate the immune system; and they secrete a host of enzymes and other compounds.[37] For example, colonic microorganisms may provide the $\beta$-glucuronidase enzymes that generate carcinogenic metabolites from compounds consumed in the diet. It has been reported that patients with colorectal cancer (CRC) have higher $\beta$-glucuronidase activity in fecal samples compared to noncancer patients.[38] In several animal models of IBD, specific bacteria have been found to be essential for developing inflammation and cancer, and in a sterile colon neither of these pathologies develops.[39] Thus, colonic microorganisms clearly are involved in the carcinogenic process. They provide protective roles

including creating a barrier to reduce interaction of toxins with the mucosal layer and induce IgA and IL10, which act as anti-inflammatory agents.[40] On the negative side, however, some intestinal microbes may act to promote cancer by inducing pro-inflammatory agents such as reactive oxygen species (ROS), IL-6, IL-17, and TNF-$\alpha$.[35]

## DIETARY BIOACTIVES AND COLONIC MICROBIOTA

The interaction between diet and the intestinal microflora directly affects the risk of colon cancer (Figure 1). For example,

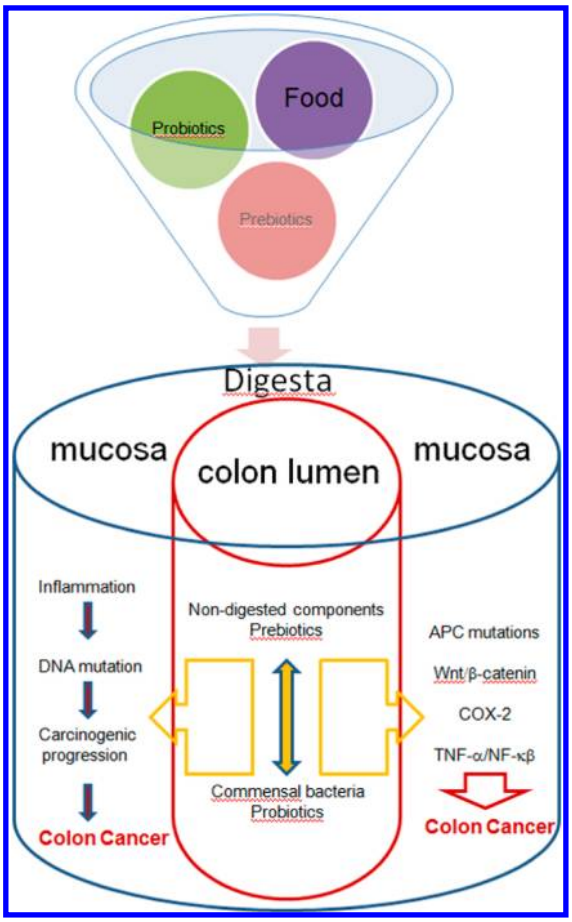


**Figure 1.** Dietary components including prebiotics and probiotics traverse the digestive process and enter the colon lumen. In the colon, complex interactions arise between the nondigested components (some of which function as prebiotics) and the bacteria (commensal as well as dietary) in the lumen, leading to production of metabolites that directly influence both cellular (left) and biochemical (right) events within the colonic mucosa. The balance of these events determines the risk for developing colon cancer.

when a high-fat diet is consumed, more bile acids are present in the colon, which can be acted upon by 7$\alpha$-hydroxylating bacteria to produce secondary bile acids, such as deoxycholic acid and lithocholic acid, which are known to be mutagenic.[41] A high-meat diet, which provides sulfur amino acids, may contribute to promoting the growth of sulfur-reducing bacteria.[42] These produce hydrogen sulfide, a toxic compound that generates free radicals, impairs cytochrome oxidase, inhibits mucus synthesis and suppresses DNA methylation, thereby increasing the risk of cancer. Fermentable compounds in the colon also generate hydrogen, which is used by methane-producing bacteria to produce methane. The role of methanogenic bacteria in colon cancer is not well described but does not seem to be strongly linked.[43] However, the beneficial effects of short-chain fatty acids (SCFA) on colon health has been well documented.[43] Butyrate and propionate likely enhance the defense mechanisms of the colon and intestinal motility. In cultured cells, buytrate induces apoptosis, decreases NF-$\kappa$B, and blocks histone hyperacetylation, which induces tumor cell growth arrest.

Among plant foods, phenolic compounds are ubiquitous and are especially high in coffee, tea, berries, nuts, vegetables, and cereals. Because plant phenolics are poorly absorbed, they may accumulate in the colon up to the millimolar range and become subjected to conversion by microorganisms into metabolites with potential biological activity. Phenolic compounds in the colon have been found to alter the microbial population by suppressing the growth of *Clostridiium* and *Bacteroides* species.[44] These compounds also may have direct effects on cancer-related events in the colon. The stilbene resveratrol has received significant attention relative to colon cancer.[45] The anti-inflammatory activity of resveratrol includes inhibition of pro-inflammatory mediators, modification of eicosanoid synthesis, and inhibition of enzymes including COX-2, NF-$\kappa$B, and AP-1, and TNF-$\alpha$, IL6, and VEGF. Rimando et al.[46] summarized studies of resveratrol in animal models of colon cancer. Most studies showed inhibition of chemically induced ACF in the colons of mice when resveratrol was given orally. However, the form of resveratrol is critically important. When transgenic alfalfa containing resveratrol glucoside was fed to mice, no inhibition of ACF was observed; however, when the diet contained the aglycone ACF, the number was reduced,[47] which suggests the glucoside may not be effective, and further illustrates the need to understand bioavailability and interaction with intestinal microorganisms. In cell culture, several phenolic compounds inhibit COX-2 activity, presumably by binding to the enzyme.[48] Whether the concentration of these compounds can be sufficiently achieved in human diets to affect these pathways is not known.

Coffee is a rich source of phenolic compounds, including caffeic and chlorogenic acids. Kang et al.[49] recently reported that coffee and caffeic acid specifically inhibited colon cancer metastasis in mice and neoplastic cell transformation by inhibiting MEK1 and TOPK and phosphorylation of ERKs. They also showed in histology samples from colon cancer patients that pERK was decreased in patients who consumed one or more cups of either regular or decaffeinated coffee. This suggests that phenolic compounds may have more specific effects and that these compounds may bind directly to target molecules, hence providing new potential therapeutic strategies.

Several animal and cell culture studies have shown that tea-derived catechins, such as epigallocatechin-3-gallate (EGCG), possess anticancer activity and mediate many cellular events that could be protective against cancer.[9,50] However, a meta-analysis of 13 human studies found a slight increase in colon cancer risk associated with tea consumption in persons consuming about four cups of tea per day.[51] The study could not distinguish the type of tea consumed. It was proposed by the authors that although tea does contain antioxidant compounds such as the catechins, other components of tea may be procarcinogenic, including nitrosamines and heterocyclic aromatic amines and tannins. Non-tea flavonoids, specifically quercetin, were suggested to provide colon cancer protection.[52] Fruits such as apples and vegetables including

onions are good sources of quercetin. Quercetin has been found to have anticancer effects including inhibition of cell proliferation and induction of apoptosis and inhibition of Cyp1A and EGFR.[53]

Probably the most promising phytochemical in cancer prevention research is curcumin.[54] Curcumin, derived from *Curcuma longa*, a member of the ginger family, has been a component of Ayurvedic practice for centuries. Many anticancer activities have been found for curcumin, including apoptotic, antiproliferative, antioxidant, and antiangiogenic properties, which make it a promising cancer therapeutic compound.[54] In an intervention study,[55] smokers with clinically detected ACF were given 2 or 4 g of curcumin orally per day for 30 days. Curcumin did not affect PGE2 or 5-HETE, in ACF or normal mucosa, and did not reduce $K_i$-67 in normal mucosa. However, the higher dose was associated with a 40% reduction in ACF number. The subjects receiving the high dose also had a significant increase in curcumin in their blood, thereby suggesting that curcumin conjugates delivered systemically may have contributed to the protective effect. It has been reported that curcumin can bind to the vitamin D receptor and activate VDR target genes such as CYP3A4, CYP24, and TRPV6 in Caco-2 cells, which may be another mechanism of action for curcumin.[56] Because curcumin has been found to mediate many important cancer pathways, clinical trials for curcumin and cancer are currently underway.[54]

## PROBIOTICS, PREBIOTICS, AND COLON CANCER

With the realization of the importance of microorganisms in the intestine, there has been substantial interest in finding beneficial microbes that will enhance health and prevent inflammation and cancer.[33] The terms prebiotic, probiotic, and synbiotic have been recently defined[57] (Table 2). The most studied probiotics have been strains of both *Lactobacillus* and *Bifidobacteria*. Probiotic species of *Lactobacillus* include *L. rhamnosus*, *L. acidophilus*, *L. plantarum*, *L. paracasei*, and *L. casei*; those of *Bifidobacterium* include *B. infantis*, *B. animalis*, *B. longum*, and *B. bifidum*. Some other probiotics include *Eschericia coli* strain Nissle 1917 and *Saccharomyces boulardii*, among others. In a recent meta-analysis, the role of probiotics in alleviating the symptoms of irritable bowel syndrome was found to be generally positive.[58] A wide range of biological responses, including influencing cell cycle and apoptosis, inhibition of enzymes, modifying immune factors, and activation of mucosal barrier components such as defensins, mucins, and trefoil factors, have been associated with probiotics.[59,60] Evidence that probiotics are beneficial for human colon cancer is limited at this time;[39] however, animal studies have shown promising effects.[61] Lactic acid bacteria have been shown to induce apoptosis and reduce hydrogen peroxide concentration in the colon as possible mechanisms that reduce colon cancer risk,[62] but it is not clear if commercially marketed probiotic products have any real efficacy.[63] Currently, characterization of the intestinal microbiome is underway, and this work should lead to improved understanding of these bacteria and how they change with diet and disease.

**Table 2. Definitions of Probiotics, Prebiotics, and Synbiotics[57]**

| | |
|---|---|
| **probiotic:** | live microorganisms that, when administered in adequate amounts, confer a beneficial health effect on the host |
| **prebiotic:** | food ingredients that cannot be digested by the human digestive system but are metabolized by discrete enteric microbes, thus stimulating proliferation of selected gastrointestinal (GI) bacteria species thought to be beneficial for human health |
| **synbiotic:** | supplement composed of a mixture of probiotics and prebiotics aimed at enhancing survival and colonization of the supplemented species in the GI tract |

Intestinal microorganisms are in constant flux depending upon the colonic environment. A major factor contributing to the relationship between host and microflora is the presence of prebiotics.[63] Prebiotics have been found to generate saccharolytic activity in the colon with SCFA as a primary product.[64] Prebiotics can lead to enhanced growth and/or survivability of selected microorganisms, which promotes changes in the overall microbial population. These changes could be protective if beneficial bacteria out-compete pathogenic ones, but the opposite may also occur. Inulin, a term that covers all $\beta$(2-1) linear fructans, is a well-characterized prebiotic.[65] Inulin stimulates colonic production of SCFA, favors the growth of *Lactobacilli* and *Bifidobacteria*, and is associated with reduced mucosal inflammation and lesion scores in a rat model of IBD.[66] Providing probiotics with selective fermentable substrates that support their growth (i.e., synbiotics) has been found to produce greater health impacts than either alone.[67,68] Prebiotics such as nondigestible carbohydrates (e.g., galacto-oligosaccharides (GOS), fructo-oligosaccharides (FOS), resistant starch, polydextrose, and inulin), dietary fibers, and conjugated fatty acids have also been investigated for their role in IBD.[69] In a European study, SYNCAN, a probiotic mixture of *Lactobacillus rhamnosus* GG (LGG) and *B. lactis* Bbl2 along with the prebiotic oligofructose-enriched inulin was administered to patients who had undergone a polypectomy or been diagnosed with CRC.[70] After 12 weeks, fecal water from the subjects given the synbiotic treatment was found to have reduced DNA-damaging capacity and colon biopsy tissue showed reduced DNA damage compared to the placebo-treated subjects.[71] This study demonstrated a protective effect of the synbiotic treatment on biomarkers of colon cancer in humans. However, few systematic assessments, using a defined mechanistic approach, have been done to characterize the relationships between pre- and probiotics on colon cancer risk. It is clearly evident that pre- and probiotics have potential to affect colonic inflammation and cancer risk, but only by characterizing these relationships will there be development of effective applications for patients.

The barrier function of the colon is critical as the first line of defense. Within the colon, the mucus layer provides the barrier for the underlying mucosal cells to inflammatory agents in the lumen. The barrier is composed of a variety of compounds, including mucus, which forms a physical deterrent to pathogens and antigens.[72] Within the mucus are a variety of compounds with specific protective functions, such as the mucins (MUC1, 2, 3, and 4) and trefoil factors (TFF 1, 2, and 3), which are secreted by goblet cells. In a rat model of colitis, feeding probiotics FOS and resistant starch individually were found to increase MUC2 in colon, but when fed together the effect was significantly greater.[73] Dietary proteins are not typically considered true prebiotics; however, there is some evidence that some proteins may provide direct or synergistic effects on colonic barrier function.[74] Spray-dried porcine plasma fed to weaning pigs provided enhanced colonic barrier and reduced inflammation.[75] Whey protein has been found to promote LGG survival in the human colon[76] and to protect rats from dextran sodium sulfate (DSS) induced inflammation.[77] These studies suggest that proteins may play a role as prebiotics for some


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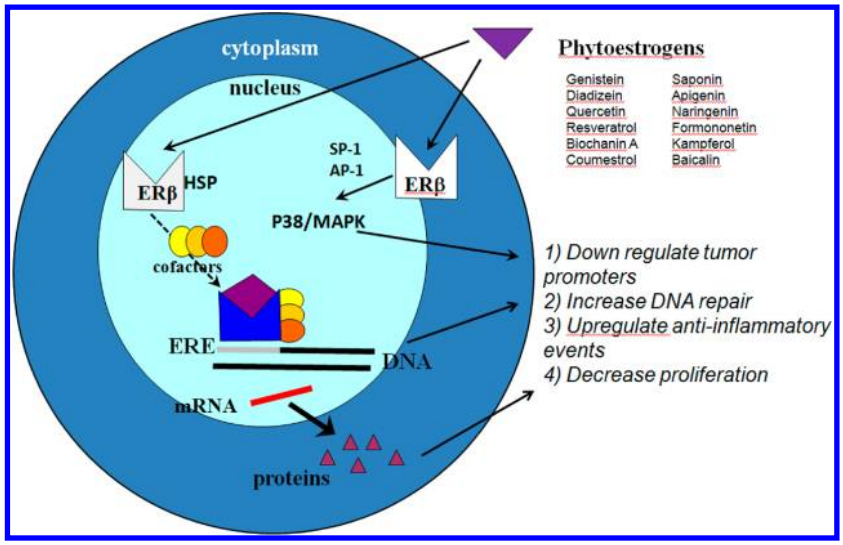


**Figure 2.** Simplified model of ER$\beta$ regulation of tumor cell growth.[83] Phytoestrogens bind to either the membrane-tethered receptors, which are associated with transcription factors SP-1 and AP-1, or nuclear receptors, which are associated with heat shock proteins (HSP). Activation of the membrane-tethered receptors is associated with rapid signaling, potentially via the p38/MAPK pathway. This leads to antiproliferative and pro-apoptotic effects. Activation of the nuclear receptor results in recruitment of cofactors that bind to estrogen receptor elements (ERE) on DNA, thereby modifying gene expression and inducing protein synthesis. The outcome of activation of ER$\beta$ in the colon is suppression of carcinogenic pathways.

probiotics, thereby creating a synbiotic relationship. In a recent study, casein, whey, and soy protein were fed to mice either with or without LGG to determine if these dietary components provided synbiotic interactions. Of the three proteins fed, only whey resulted in a high level of LGG in the cecum of the mice, which suggests a protective role of whey protein on the survival of the probiotic through the digestion process. Mice treated with DSS had increased MUC1 expression in the colon when fed casein, regardless of LGG treatment. MUC1 expression was also increased by DSS in mice fed whey without LGG but was not increased when LGG was fed, suggesting a protective effect of the probiotic on MUC1. Mice fed soy and treated with DSS had MUC1 expression levels similar to those fed casein without DSS, regardless of LGG. Overall, the mice fed soy and treated with DSS had barrier protein expression similar to that of the casein-fed mice not treated with DSS, thereby suggesting a protective effect of soy protein independent of the probiotic. Soy components, such as lunasin,[78] fiber,[79] and isoflavones,[80] have been found to reduce inflammation and cancer in animal models. This and other studies clearly demonstrate that diet composition affects probiotic survival, that a wide variety of food components may influence colonic barrier function, and that future work needs to thoughtfully incorporate the interconnectedness of the colonic microbiome with diet and the disease process.

## ■ ESTROGENIC BIOACTIVES AND COLON CANCER

A current interest in colon cancer regulation is the role of estrogen.[81,82] Estrogen and the estrogen receptors ER$\alpha$ and ER$\beta$ mediate a plethora of biological responses and participate in the initiation and progression of cancers.[83] Several dietary bioactive compounds directly interact with the estrogen receptors. The response of a given cell to estrogen activation is dependent upon the relative proportion of the two subtypes and downstream regulators. The most well-defined events associated with estrogen receptors are the genomic responses in which activation of the ligand-binding domain leads to conformational change in the receptors, nuclear translocation, and binding to estrogen response elements on DNA. However, many effects of estrogen can have a more rapid onset. These events, presumably mediated by membrane-tethered receptors, signal cell proliferation (ER$\alpha$) or antiproliferation (ER$\beta$).[84] Within cancer cells there is substantial evidence that the nongenomic regulation of cell cycle events by estrogens is important. Although colon cancer is common in both men and women, an early hypothesis suggested the incidence of colon cancer in premenopausal women was actually lower than in age-matched men.[85] After menopause, this difference disappears, and because colon cancer is more common in older adults, the link with estrogen was not as obvious. However, over the past decade there has been growing evidence that ER$\beta$ is a dominant factor in the colon, with expression throughout the intestinal tract.[86,87] From studies of colon tumors and in cultured cells, it has been shown that the loss of ER$\beta$ is associated with uncontrolled cell growth, failure in cell differentiation, and decreased apoptosis.[88,89] For these reasons ER$\beta$ is now a prime target for colon cancer therapy, as are compounds that interact with ER$\beta$.[90]

Phytoestrogens in the diet have been proposed to play a role in colon cancer.[80] Using ER$\alpha$KO mice, it has been shown that the phytoestrogen genistein, derived from soy, altered colon cancer progression, presumably through ER$\beta$. Genistein is the most abundant phytoestrogen in soy and is structurally similar to 17$\beta$-estradiol. Two other phytoestrogens, daidzein and glycitein, are also present in soy and have weak estrogenic activity. Several studies have demonstrated that phytoestrogens such as genistein[91] or ER$\beta$-specific antagonists[92] mediate colon cancer. Acting as a selective estrogen receptor modulator, resveratrol may also affect colon cancer via the estrogen receptor.[90] Using in vitro assays,[93] it was found that quercetin binds to ER$\alpha$ as an estradiol antagonist and also binds to ER$\beta$, leading to apoptosis. Dietary lignans, found in whole grains, have also been found to possess estrogenic activity, which may be one mechanism through which these foods reduce colon cancer risk.[94] It is not fully clear whether these phytoestrogen


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compounds activate the genomic or nongenomic receptors; however, the role of ER$\beta$ in colon cancer is now well accepted.[95] The evidence that ER$\beta$ provides a protective effect against colon cancer is strong, and development of therapies targeting ER$\beta$ is likely.[96] However, there is currently no understanding of how phytoestrogens may interact with the colonic microbiome. Given the potential for phytochemicals to selectively interact with this receptor, there is a promising role for dietary components in colon cancer prevention via this mechanism (Figure 2). More research is needed to understand fully the role of ER$\beta$ and how phytochemicals modulate its activity.

In summary, the very important interactions among dietary components and the intestinal microbiome in mediating colon cancer risk are now clearly evident. Future research of the role of dietary components in colon cancer must be carefully designed to ensure these relationships are fully considered. There are likely to be many phytochemicals with important anticancer potential, and curcumin is a prime example that is now in clinical trials. The role of estrogen receptors, especially ER$\beta$, in colon cancer is increasingly being understood and provides another target for dietary bioactive components.

## AUTHOR INFORMATION


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### Notes

The authors declare no competing financial interest.

## ABBREVIATIONS USED

ACF, aberrent crypt foci; CRC, colorectal cancer; DSS, dextran sodium sulfate; ECGC, epigallocatechin gallate; ER$\alpha$, ER$\beta$, estrogen receptor alpha and beta; FAP, familial adenomatous polyposis; FOS, fructo-oligosaccharides; GOS, gluco-oligosaccharides; HNPCC, hereditary nonpolyposis colorectal cancer; IBD, inflammatory bowel disease; MUC, mucin; ROS, reactive oxygen species; SCFA, short-chain fatty acids; TFF, trefoil factor.

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