Colorectal Cancer Prevention with a Plant-Based Diet

Stewart Rose* and Amanda Strombom

Plant-Based Diets in Medicine, USA

Submission: October 13, 2019; Published: October 24, 2019

*Correspondence Author: Stewart Rose, Plant-Based Diets in Medicine, 12819 SE 38th St, #427, Bellevue, WA 98006, USA

Abstract

A plant-based diet is valuable in the primary and secondary prevention of colorectal cancer. Epidemiological studies show a 46%-88% reduced risk of colorectal cancer for those following a plant-based diet. In light of evidence, the World Health Organization International Agency for Research on Cancer (IARC) has classified processed meat as a carcinogen and red meat as a probable carcinogen and has since reaffirmed their decision in light of more recent studies. The pathogenic mechanisms by which processed and red meat can cause colon cancer to have been determined. Several exogenous carcinogens are contained in meat and others are formed as a byproduct of its preparation. Bacterial flora produces several carcinogens endogenously in response to processed and red meat intake. Some of the ways plant foods and their phytonutrients protect against colon cancer are also now understood. The chemoprotective mechanisms of plant foods are through the direct actions of phytochemicals, through the action of fiber, and as a result of the anti-inflammatory environment produced by the colonic flora. While colonoscopy and FIT-DNA tests remain very valuable for secondary prevention, a plant-based diet can provide both primary and secondary prevention of colorectal cancer. Making prevention of colon cancer with a plant-based diet all the more desirable is that it is also a safe and efficacious prophylaxis and treats common comorbidities such as coronary artery disease and type II diabetes.

Keywords: Anti-Inflammatory; Bacterial Flora; Carcinogens; Colorectal Cancer; Diet; Fiber, Phytochemicals; Plant-Based Diet; Vegetarian, Vegan

Introduction

This review article takes a comprehensive look at the research currently available on the potential of diet to impact the primary and secondary prevention of colorectal cancer. It does not cover fewer common pathologies such as Familial Adenomatous Polyposis, Turcot Syndrome and Lynch Syndrome.

Prevention of Colorectal Cancer

General Epidemiology

Only 5-10% of all cancer cases can be attributed to genetic defects, whereas the remaining 90-95% have their roots in the environment and lifestyle. The lifestyle factors include cigarette smoking, diet - especially meat - alcohol, sun exposure, environmental pollutants, infections, stress, obesity, and physical inactivity. (1). The link between diet and cancer is revealed by the large variation in rates of specific cancers in various countries, and by the observed changes in the incidence of cancer in migrating. For example, East Asians have been shown to have a 25 times lower rate of many forms of cancer, but these rates increase substantially in individuals who migrate to the West [1]. Since genetics don't change with migration, but diet usually does, the increase is most likely attributable to adopting the Standard American Diet. While some lifestyle factors, such as cigarette smoking, are now well acknowledged as affecting cancer, the role of diet is less well known. However, diet may be linked to as many as 70% - 80% of cases of colorectal cancer [2-6]. What's more, we know which type of diet is the most beneficial. A Canadian study showed that a plant-based diet resulted in a 46% decreased risk of colon cancer and 73% decreased risk of rectal cancer [7].

Literally hundreds of studies have been conducted addressing the relationship of some type of plant foods or plant food constituents and cancer risk. A clear majority of these studies demonstrate that fruits, vegetables, legumes, whole grains, tree nuts, spices, and seeds, as well as specific types of food within these categories including citrus fruit, tomatoes, cruciferous vegetables, soybeans, and wheat, for example, reduce the risk of one or more types of cancer [8-11]. On the other hand, a number of studies have examined relationships between processed and red meat intake and colorectal cancer, many of which have been summarized in at least one of four meta-analyses over the past decade [8,12-14]. A systematic review and meta-analysis of epidemiological studies relating the amount of processed and red meat consumed to increased risk of colon cancer showed that processed meat increased the risk of colon cancer by 58% per 100gm and red meat increased the risk of colorectal adenoma by 27% per 100gm [15].
One particularly large, general food study, using data from the EPIC (European Prospective Investigation into Cancer) study, also showed an increased risk of colon cancer associated with processed and red meat consumption. Those consuming the most processed and red meat had a 35% increased risk of colorectal cancer (CRC) overall. This study also found a 55% increased risk per 100 g of processed meat and a 25% increased risk of CRC per 100 g increase in red meat. No increased risk was found for poultry intake, and there was an inverse association with fish intake, but note that the risks were not being measured against a plant-based diet, only against varying levels of meat and fish consumption [16].

It has been well documented that most colorectal cancers arise from colorectal adenoma by a process referred to as the adenoma–canceroma sequence [17]. Thus, identification of modifiable risk factors for colorectal adenoma is also helpful for modifying the correctable risk of colorectal adenoma and preventing colorectal cancer. In a study comparing Buddhist priests, who are obligatory vegetarians, with matched controls, the risk of colon adenoma was 54% higher in non-vegetarians than in vegetarians. The risk for advanced adenoma was over 3 times higher in non-vegetarians than in vegetarians [18]. These results are especially notable because the meat intake of the non-vegetarians was relatively low. Vegetarian and vegan diets increase beneficial plant foods and plant constituents, eliminate the intake of red and processed meat, and aid in achieving and maintaining a healthy weight. The direct and indirect evidence taken together suggests that vegetarian diets are a useful strategy for reducing the risk of colon cancer [2].

This has been tested in a couple of significant studies. In a 6-year prospective study of people who otherwise have a healthy lifestyle, meat eaters had an 88% increased risk of colon cancer compared to long term vegetarians. In this study by Fraser et al, in contrast to other studies, white meat raised the risk of colon cancer at least as much as red meat. Those who ate legumes more than twice a week had a 47% decreased risk of colon cancer. Those with a high meat diet and low legume consumption, and who had an above normal BMI, had a threefold increased risk of colon cancer [19].

In another study, Orlich et al. found that a plant-based diet offers a 49% decreased risk of colon cancer, compared with a typical American high meat diet [20]. According to the author, the meat-eaters in this study were consuming less than 2 oz of meat a day, and so were already 27% less likely to get colon cancer. His results showed that those following the vegetarian diet had an additional 22% decreased risk of colon cancer compared to these meat eaters, so adding these factors together gave a 49% decreased risk. This study had some other significant limitations. Those following a plant-based diet had been doing so for less than half the amount of time the meat eaters were following their diet, and were also older, on average, than the meat eaters. This study did not compensate for these factors. Taking these limitations into account, it is possible that even better results could be obtained [20].

**Risk Factors for Colon Cancer**

Age is a significant risk factor for colon cancer, but it is clearly unmodifiable. Alcohol consumption and cigarette smoking are also well-recognized, modifiable risk factors. Here we consider diet-related and other modifiable risk factors.

**Dietary Risk Factors**

In October 2015, processed meat was classified by the World Health Organization International Agency for Research on Cancer (IARC) as carcinogenic to humans (Group 1), based on strength of evidence in humans that the consumption of processed meat causes colorectal cancer [21]. Red meat was classified as probably carcinogenic to humans (Group 2A) [21]. New epidemiological studies and reviews have been published since then, clearly supporting the IARC decision [22].

**Hyperinsulinemia**

A number of epidemiological studies have consistently demonstrated that the risk for several types of cancer (including that of the breast, colorectum, liver, and pancreas) is higher in insulin-resistant patients [23]. Metabolic syndrome increases both insulin and insulin resistance, due to high body mass, high saturated fat intake, and high glycemic load, a synergism that implicates hyperinsulimetic exposure in colon carcinogenesis [2,19]. Vegetarians have a 70-80% reduced risk of hyperinsulinemia [24] and lower insulin levels [25,26]. This likely is one of the factors causing their reduced risk of colon cancer.

**Obesity**

High body mass index (BMI) is a risk factor for colon cancer [27]. Vegetarians and vegans have significantly lower BMI’s on average. A study of American vegetarians and vegans found that that vegetarians had a mean BMI of 25.7 and vegans a mean BMI of 23.6 [28]. A European study found the average BMI of vegetarians and vegans to be 23.3 and 22.4 respectively for men and 22.8 and 21.8 for women [29]. A study of German vegans found an average BMI of 22.3 [30]. A study of vegetarian children found that they too had lower BMI’s than their meat-eating counterparts with an average BMI of 17.3 in ages 6 to 11 and average of 20.0 ages 12-18 [31]. One study found the risk of being overweight or obese is 65% less for vegans and 46% less for vegetarians [32].

**Crohn’s Disease**

There is an elevated risk of colon cancer in patients with Crohn’s Disease [33]. However, a vegetarian diet reduces risk of Crohn’s disease by 70% in girls, and 80% in boys [34]. Therefore, a vegetarian diet reduces the risk of colon cancer by reducing the consumption of red and processed meat, and reducing the risk of hyperinsulinemia, obesity and Crohn’s Disease.
Preventative Factors from Food

Epidemiologic studies have shown that the consumption of foods of plant origin is associated with lower risk of several cancers, including Colorectal Cancer (CRC) [8]. The specific constituents in the dietary foods which are responsible for helping to prevent CRC and the possible mechanisms have also been investigated extensively. Various phytochemicals have been identified in fruits, vegetables, grains, nuts, and spices which exhibit chemo-preventive activity [35]. They have various cancer impeding activities, such as reducing DNA damage via antioxidant properties or interacting with inflammation pathways [36]. In this article we focus on just two phytochemicals as examples, sulforaphane and salicylate. However, there are many others that have chemo-protective effects.

Sulforaphane

Sulforaphane (SFN) is an isothiocyanate that is naturally present in cruciferous vegetables, with high concentration in broccoli. The results of the most recent studies indicate that multi-targeted sulforaphane actions may contribute to prevention and treatment of cancer. Protective properties of sulforaphane have been observed in every stage of carcinogenesis [7]. Due to their increased consumption of cruciferous vegetables, vegetarians will benefit from the protective properties of sulforaphane more than meat-eaters.

Salicylates

The role of aspirin in cancer has been extensively investigated [37,38]. Aspirin use is associated with decreased risk for colorectal, breast, esophageal, lung, stomach and ovarian cancer, and aspirin is both a chemo-preventive and chemo-therapeutic agent for breast and colon cancer [39-43]. A recent report on the chemo-preventive effects of aspirin showed that the incidence of colon cancer in Scotland was significantly decreased in the general population at the lowest daily dose of aspirin (75 mg), and that the decreased incidence was observed even after only 5 years of aspirin use [42]. Regular aspirin use after the diagnosis of colorectal cancer is associated with lower risk of colorectal cancer-specific and overall mortality, especially among individuals with colon cancer tumors that overexpress Cyclooxygenase 2 (2 COX-2) [40].

After absorption, aspirin is very rapidly hydrolyzed to salicylic acid (2-hydroxybenzoic acid) [44]. The reported high serum salicylate/aspirin ratios observed in human studies using aspirin suggest that salicylate may be an important contributor to the anticancer activity of aspirin, especially in colon cancer patients. Salicylates are widely distributed throughout the plant kingdom, and they are therefore present in plant products of dietary relevance, such as fruit, vegetables, herbs and spices. Moreover, they appear to be readily absorbed from the food matrix. This has led some to suggest that the recognized effects of consuming fruit and vegetables on lowering the risk of several diseases, such as colon cancer, may be due, in part, to salicylates in plant-based foods [45,46].

Fiber

Inverse associations between dietary fiber intake and colorectal cancer risk have been reported in ecological and case-control studies [47,48]. Inverse associations for fiber and colorectal adenoma [49] and colorectal cancer [50-53] have also been reported in well-designed prospective studies. In the EPIC study, after an average follow-up of 6.2 years and 1,721 colorectal cancer cases, a 21% reduced risk amongst participants in the highest fiber intake quintile was observed when compared against the lowest intake group [54,55]. In a recent systematic review, in which a high concordance between study results was observed, the World Cancer Research Fund/American Institute for Cancer Research panel upgraded the association between fiber and colorectal cancer to “Convincing” [56]. Vegetarians and vegans, consuming a wide variety of plant-based foods, will naturally consume much more fiber than meat-eaters.

Pathophysiology

Research on the prevention of colon cancer with a vegetarian diet has gone beyond epidemiologic association. We now know of several mechanisms by which red and processed meat causes colon cancer and certain constituents of plant foods (phytonutrients) that help prevent it. For each of these mechanisms, vegetarians carry a distinct advantage. This helps explain why the risk of colon cancer is substantially lower in those who follow a plant-based diet.

1. Carcinogens such as:
   a. heterocyclic amines (HCAs),
   b. poly-aromatic hydrocarbons (PAHS)
   c. nitrites, and
   d. poly-chlorinated biphenyls (PCBs)

2. Insulin

3. Insulin-like Growth Factor (IGF)

4. Inflammation, as indicated by C-Reactive Protein (CRP)

5. Matrix metalloproteinases (MMPs)

Protective phytonutrients explained below include:

1. Salicylates
2. Sulforaphane
3. Phytic Acid and
4. Fiber

The microbiome also has a role in the pathogenesis of colon cancer. Heme iron promotes the bacterial production of Nitroso amines which are known carcinogens. While a meat-centered diet promotes the growth of bacteria which have an inflammatory action in the colon, a vegetarian diet results in a different composition of flora, favoring the growth of bacteria...
that produce anti-inflammatory metabolic byproducts such as butyrate.

**Pathogenic Mechanisms**

**Carcinogens**

Several individual compounds have been suggested to explain the underlying mechanisms by which red and processed meat may increase the risk of colorectal cancer, including heme iron [57,58], heterocyclic amines (HCAs) [57,59], polycyclic aromatic hydrocarbons (PAHs), [60] nitrates and nitrates [57,61], and organochlorine compounds such as PCBs [62]. HCAs, PAHs, nitrates and nitrates may all be involved in colorectal cancer etiology [63]. Heme iron is a pro carcinogen that becomes a carcinogen as a result of bacterial transformation to nitroso amines. Although there some preformed nitroso amine in the diet, the majority is produced by intestinal flora. Therefore, the role of heme iron in that pathogenesis of colon cancer will be discussed in the microbiome section (The Role of the Microbiome in the Pathogenesis of Colon Cancer).

Heterocyclic amines are mutagenic compounds formed when muscle meat is cooked using high-temperature methods, such as grilling, barbequing, and pan-frying [64]. They are formed when amino acids, sugars, and creatine react at high temperatures, especially those above 150 degrees Celsius. Cooking methods that result in the greatest amounts of HCAs include grilling and pan-frying [65].

HCAs, measured using urine or leukocyte assays, have been associated with colon adenoma [66-69]. Many studies, examining interactions between meat intake and genetic polymorphisms that modulate metabolism of HCAs, also provide indirect yet compelling support for an association between these carcinogens and colorectal neoplasia [69-78]. In one study, women with genotypes associated with rapid acetylation of meat-associated carcinogens, had a particularly high risk of colorectal cancer [79]. This strongly points to heterocyclic amines as carcinogenic for colon cancer.

Polycyclic aromatic hydrocarbons (PAHs) are well known to be carcinogenic. They are produced in many industrial situations, burning coal and wood, and by smoking cigarettes, but for a non-smoking person who hasn't been exposed to industrial processes, the prime source of PAHs comes through the diet. Some PAHs are deposited on plant foods through air pollution, which then bio-concentrate in animal adipose tissue through animals’ consumption of plant foods over their lifespan, leading to much higher levels in animal tissue than in plant foods. However, the primary source of PAHs in the diet is as a result of thermal treatment of meat, especially barbecuing or grilling [80,81].

Meat that is cooked above an open flame, as with grilling and barbequing, results in fat and juices dripping onto the fire, yielding flames that contain PAHs. These PAHs then adhere to the surface of the meat [65]. The smoking of meat, or other food preparation methods that expose meat to smoke or charring, also contributes to PAH formation. As an important human exposure pathway of contaminants, dietary intake of PAHs is of increasing concern for assessing cancer risk in the human body [82]. Studies of PAH exposure indicate that the target organs for PAH compounds are the lung, oropharynx, breast and genitourinary and gastrointestinal tracts [83]. Dietary PAHs are of special concern to cancer of the gastrointestinal tract. In humans, there is specific evidence for the association of dietary PAH exposure with colon cancer [84,85].

The following significant positive associations were observed for meat-related PAH compounds: 2-amino-3,4,8-trimethylimidazo[4,5-f]quinoxaline (DiMeIQx) and colorectal, distal colon, and rectal tumors; 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline (MeIQx) and colorectal and colon cancer tumors; 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) and rectal cancer; and benzo[a]pyrene and rectal cancer [63]. One study determined a profile of 14 PAHs, frequently found in food: in cow’s milk, human breast milk, and meat- and fish-based foods. The levels of PAHs were much higher than the permissible limits of 1 μg/kg in a large percentage of the foods sampled [86]. Sodium nitrates and nitrates are added to meat for preservation and curing purposes. They are commonly found in processed meat products, such as ham, bacon, salami and hot dogs. These nitrates and nitrates that are readily converted to nitrites by bacteria—react with amines or amides derived from protein, leading to the formation of N-nitroso compounds (NOCs), which are potent carcinogens [61,87]. See section The Role of the Microbiome in the Pathogenesis of Colon Cancer for more information on this process.

Organochlorine compounds, such as polychlorinated biphenyl (PCB) and organochlorine pesticides, have also been linked to increased risk of several cancers. Despite reductions in their use in the developed world, they remain one of the most important groups of persistent pollutants to which humans are exposed, primarily through dietary intake. They are deposited on plant foods through polluted water and air; but due to bioaccumulation in fatty tissue, meat and dairy products contain much greater levels of such compounds than plant products [88-90]. Some PCBs are not absorbed in the intestine and remain in the stool, potentially damaging the colon. A study found that an elevated risk of colorectal cancer was positively associated with the consumption of mono-ortho PCB congeners 28 and 118 in the diet [62]. Another way that meat acts as carcinogen is in its activation of Toll Like Receptors (TLRs). A study showed that meat intake may activate TLRs at the epithelial surface. This can lead to colorectal cancer via nuclear factor-kB-initiated transcription of inflammatory genes. However, intake of fiber may protect against colorectal cancer via TLR4-mediated secretion of interleukin-10 and cyclooxygenase-2 [91].

**Hyperinsulinemia**
Insulin resistance is a pathological condition in which insulin action is impaired in peripheral target tissues including skeletal muscle, liver, and adipose tissue. Initially, in individuals destined to develop Type 2 Diabetes, the pancreatic beta cells increase insulin production to overcome insulin resistance and maintain euglycemia [92]. Hyperinsulinemia promotes colon carcinogenesis, since insulin is an important growth factor of colonic epithelial cells and is a mitogen of tumor cell growth in vitro [93]. Insulin can exert its oncogenic potential via abnormal stimulation of multiple cellular signaling cascades, enhancing growth factor-dependent cell proliferation and/or by directly affecting cell metabolism [92]. Insulin also increases the bioactivity of IGF-I by enhancing hepatic IGF-I synthesis and by reducing hepatic protein production of the insulin-like growth factor binding proteins 1 and 2 (IGFBP-1 and IGFBP-2) [94,95]. Therefore, although insulin can directly induce tumor growth, many of its mitogenic and antiapoptotic effects are operating through the IGF-I system, as reported in individuals with high levels of circulating IGF-I, in which an increased risk of developing certain types of tumors [95,96].

To date, two insulin receptor (IR) isoforms have been described. They differ in the presence of a short exon 11 that can be excised from (IR-A, short isoform) or included in (IR-B, long isoform) the IR coding sequence as a result of alternative splicing [97,98]. While glucose uptake remains the main IR-mediated function, a growing body of evidence suggests that the two IR isoforms have different biological roles with IR-A mostly exerting mitogenic effects and IR-B modulating cell metabolism [99]. Males with serum C-peptide concentration >3.3 ng/mL were 3.8 times more likely to have an adenoma relative to no polyp than those with C-peptide ≤1.8 ng/mL [100]. As therefore would be expected, serum insulin levels directly correlate with the presence of adenoma and hyperplastic polyps in the proximal colon, and also, but less strongly, correlate with the presence of distal adenoma [101].

Insulin-Like Growth Factor

The insulin-like growth factor (IGF) system is a multifactorial signaling network that modulates energy metabolism, cell growth, and cancer [97]. (97) IGFs are potent proliferation stimulators for numerous tumor cells and often function as autocrine growth factors. It has been shown that IGF-I and IGF-II enhance proliferation of colorectal carcinoma cells. The biological signal of both factors is transmitted through the IGF-I receptor (IGF-I-R) [102].

Breast, ovarian, prostate, lung, and colon cancer are the tumor tissues where the IGF system has been directly linked to tumor development and progression [103,104]. As explained above, hyperinsulinemia makes IGF even more damaging. The insulin/IGF biochemical system has also been associated with tumor formation and progression in breast, ovarian, prostate, lung, and colon cancer, especially the sporadic form of colorectal carcinoma that emerges through the adenoma–carcinoma pathway [103-105]. Hyperinsulinemia has an effect on cell proliferation, not only through insulin receptor signaling, but also through the amplification of IGF-1 effect [105,106]. IR-A receptors are overexpressed in tumors cells and both insulin and IGF-1 through its effect on HR/IR-A enhance cell proliferation. An overexpression of IGF receptors was found in human colon cancer cells, which was later on associated with formation of IRS-1 and IRS-2, and subsequently Akt activation and up regulation of the anti-apoptotic protein Bcl-xL, as well as activation of β-catenin and its translocation into the nucleus, and subsequent promotion of cell proliferation gene transcription.

In a study comparing vegan women with meat-eating women, the mean serum IGF-I concentration was 13% lower in vegan women compared with meat-eaters. In line with these lower levels, the mean concentrations of both serum IGF-binding protein (IGFBP)-1 and IGFBP-2 were 20–40% higher in vegan women compared with meat-eaters [107]. Similar results have been obtained studying vegan men [108].

C-Reactive Protein (CRP)

Cardio Reactive Protein (CRP), whose levels are of use in cardiology, also happens to be valuable as a prognostic factor in colon cancer. CRP is correlated with colon cancer prognosis and risk of death in colon cancer. One study showed a stage specific increase in poor prognosis and increased risk of death for high CRP levels: 7.37 for stage I and II, 3.29 for stage III, and 2.24 for stage IV [109]. A study of CRP and adenoma showed a positive association between plasma CRP concentration and the prevalence of colorectal adenoma [110]. Given that CRP is a preferable biomarker of systemic inflammation and a highly sensitive method that can evaluate low-grade inflammation, this finding of a positive association between higher CRP levels and an increased prevalence of adenoma supports the hypothesis that the development/growth of colorectal neoplasia likely involves a systemic, low-grade inflammatory state.

In another study, a dose response relationship with CRP level was observed for risk of multiple small tubular adenomas, increasing the risk 101% for the highest vs lowest tertile comparison, and increasing the risk of advanced adenomas by 81% for highest vs lowest tertile comparison [111]. An elevated CRP is particularly associated with increased risk of colorectal cancer in patients with inflammatory bowel disease. A study showed an increased risk of colorectal cancer across quartiles of CRP elevation, with an increased risk of almost 200% for the highest versus the lowest quartile [112]. The ability of a plant-based diet to lower CRP levels, and the fact that vegetarians have lower CRP levels [113], is very relevant to colorectal cancer risk. Lower levels of hs-CRP were found in those following a vegetarian diet for more than 2 years [114]. The fact that vegetarians have lower levels of CRP decreases their chance of a poor prognosis for colon cancer.
Matrix metalloproteinases (MMPs) consist of a multigene family of zinc-dependent extracellular matrix (ECM) remodeling endoproteinases implicated in pathological processes, such as carcinogenesis. In this regard, their activity plays a pivotal role in tumor growth and the multistep processes of invasion and metastasis, including proteolytic degradation of ECM, alteration of the cell-cell and cell-ECM interactions, migration and angiogenesis [115]. Considerable evidence has implicated the over expression of matrix metalloproteinases (MMPs) MMP-1, -2, -3, -7, -9, -13 in human colorectal cancers. The degree of over expression of some MMPs has been noted to correlate with stage of disease and prognosis [116,117]. One study examined circulating plasma concentrations of myeloperoxidase (MPO), matrix metalloproteinases MMP-9 and MMP-2, and tissue inhibitors of MMP TIMP-1 and TIMP-2, between healthy vegetarians and healthy omnivores. The study found significantly lower concentrations of MPO, MMP-9, MMP-2 and MMP-9/TIMP-1 ratio in vegetarians compared to omnivores [116,117].

**Protective Mechanisms**

Several phytonutrients found in plant foods have chemo-protective properties. While the number of different phytonutrients is considerable, in this section we consider some of the more important ones as examples, sulforaphane, salicylate, phytic acid (inositol hexaphosphate), and fiber.

**Sulforaphane**

Various Brassica vegetables, especially broccoli, contain glucoraphanin (sulforaphane or SFN). Following cutting or chewing, it is hydrolyzed into the corresponding isothiocyanate SFN either by the plant thioglucosidase myrosinase or by bacterial thioglucosidases in the colon [118]. Because of its lipophilicity [119] and molecular size, SFN is likely to passively diffuse into the enterocytes [120]. After absorption, SFN is conjugated with glutathione (SF-GSH) by glutathione-S-transferase (GST) leading to maintenance of a concentration gradient and facilitating a fast passive absorption into the cell [121]. It is metabolized via the mercapturic acid pathway, producing predominantly cysteinylglycine (SF-CG), cysteine (SF-Cys), and N-acetyl-cysteine (SF-NAC) conjugates that are excreted in the urine [122].

The mechanism of protection against the initiation of carcinogenesis by SFN includes modulation of phase I and II xenobiotic metabolizing enzymes, as well as direct blocking of specific binding sites of carcinogens with the DNA molecule. As a result, SFN inhibits DNA adduct formation, thus reducing the risk of mutations. Further SFN activity is targeted at cancer cells and prevents their expansion due to regulation of proliferation and induction of differentiation and/or apoptosis. In vitro studies using various types of cancer cells have revealed the ability of SFN to arrest the cell cycle, particularly in G2/M, while SFN at higher concentration is shown to activate apoptotic pathways. The possible SFN anticancer effect in the progression stage of carcinogenesis has been proven by a few studies, which provide evidence for its anti-angiogenic and anti-metastatic influence. Additionally, SFN exhibits anti-inflammatory effects relevant to cancer prevention [123].

The induction of cell cycle arrest and apoptosis is a key mechanism by which SFN exerts its colon cancer prevention effects on the growth and viability of Human Carcinoma Cells (HT29 cells) during their exponential growing phase [124]. It was observed that sulforaphane induced a cell cycle arrest in a dose dependent manner, followed by cell death. Moreover, the weak effect observed on differentiated Human Colon cells (CaCo2 cells) suggests a specific anticancer activity for this compound [125].

**Salicylates**

The cancer preventive action of aspirin is due to its principal metabolite, salicylic acid. Sodium salicylate induces apoptosis in cancer cells [126]. Regular ingestion of aspirin can prevent cancer: observational studies, randomized polyp prevention studies, long-term cancer follow-up in cardiovascular aspirin trials and randomized trials with cancer as an endpoint confirm this relationship [127]. The first successful, double-blind randomized, controlled trial of aspirin chemoprevention (Cancer Prevention Programme–CAPP2) was carried out in 1009 carriers of Lynch syndrome (hereditary CRC) [127]. Two aspirins taken daily for two years reduced CRC by more than 50% five years later. Obese participants were particularly protected [128].

Aspirin’s anti-neoplastic effects are generally attributed to salicylic acid inhibiting prostaglandin G/H-synthase 2 (PGHS2, commonly termed COX2) transcription, preventing PGHS2 from converting arachidonic acid to potentially tumor inducing prostaglandins. Aspirin down regulates Sp1, Sp3 and Sp4 transcription factors, reducing expression of proteins including VEGF (vascular epithelial growth factor), reducing tumor cell growth [129]. Additionally, aspirin may only be beneficial in CRCs characterized by a mutated, rather than wild type PIK3CA gene, explaining the effects of aspirin, independently of non-steroidal anti-inflammatory (NSAID) use [130]. Even 100 nmol/ml has an effect. Assuming salicylic acid is the anti-neoplastic component in aspirin, inhibition of COX2 cannot be the only mechanism by which aspirin prevent cancers, because the anti-neoplastic effect of NSAID drugs does not vary in direct relation to COX2 inhibition. The inhibition and induction by salicylates include the following:

(i) The interruption of nuclear factor kappa B (NF-κB),

(ii) The interruption of extracellular signal-regulated kinases,

(iii) The induction of caspase 8 and 9, and

(iv) The inhibition of β-catenin signaling mechanism.

These are therefore the mechanisms by which salicylates...
Dietary salicylates can have the same effect [46,132]. Median serum concentration in vegetarians not taking aspirin drugs is 107 nmol/ml; showing that diet can elevate serum salicylate levels enough to decrease COX2. In a study comparing vegetarians with meat-eaters taking 75mg of aspirin daily, some of the vegetarians achieved a serum salicylic acid level equal to those taking aspirin [133]. Lawrence et. al. show that urinary excretion of salicyluric acid (SU) and salicylic acid (SA) is significantly increased in vegetarians compared with non-vegetarians [134]. They previously reported that serum salicylic acid was also significantly increased in vegetarians compared with non-vegetarians [133]. Interestingly, urinary excretion of SA was similar in vegetarians and patients consuming 75 or 150 mg of aspirin/day, although SU excretion was substantially greater in the aspirin groups. It should also be noted that while studies of salicylate and colon cancer often use a time period of five to ten years, vegetarians, and even more so vegans, have often been consuming salicylate rich foods for much longer or even their whole lives.

### Phytic Acid

Most of the research on the effects of phytic acid to prevent colon cancer has been in vitro on both human and animal cells and in vivo in rats, with just one in vivo study in humans. While they therefore must be interpreted with caution, there is a significant amount of research to indicate the likelihood that phytic acid has chemoprotective activity against colon cancer through several mechanisms. Recently phytic acid (inositol hexaphosphate or IP₆) has received much attention for its role in cancer prevention and control of experimental tumor growth, progression, and metastasis. Exogenously administered IP₆ is rapidly taken up into the cells and dephosphorylated to lower inositol phosphates, which affect signal transduction pathways resulting in cell cycle arrest. A strong anticancer action of IP₆ was demonstrated in different experimental models. In addition to reducing cell proliferation, IP₆ also induces differentiation of malignant cells. Enhanced immunity and antioxidant properties also contribute to tumor cell destruction [135].

IP₆ has been demonstrated to exert valuable anticancer effects in vivo when administered to cancer patients. An antitumor activity has been observed in advanced colon cancer patients, where inositol treatment is associated with appreciable reduction in tumor burden and improved quality of life. Moreover, if inositol was added along with conventional chemotherapy, colon cancer patients experienced significantly less side effects than controls, as reported in a pilot study [136]. One mechanism by which IP₆ is chemoprotective is through modulating the gene expression. The results of a study show that IP₆ modulates MMP-2, TIMP-1 and TIMP-2 genes expression in human colon cancer cells at the transcriptional level in a way dependent on its concentration and time of interaction [137].

Phytochemicals such as phytic acid might suppress oxidant damage to intestinal epithelium. Inasmuch as colonic bacteria can produce oxygen radicals in appreciable amounts, dietary phytic acid can act as a potent anticancer agent [140]. These are elements of rapidly accumulating data from animal models, indicating that dietary supplementation with phytic acid may provide substantial protection against experimentally induced colon cancer. Should further investigations yield additional support for this hypothesis, purposeful amplification of dietary phytic acid content would represent a simple method for reducing the risk of colon carcinogenesis [138].

Preliminary studies in humans show that IP₆ and inositol, the precursor molecule of IP₆, appear to enhance the anticancer effect of conventional chemotherapy, control cancer metastases, and improve quality of life. Because it is efficiently absorbed from the gastrointestinal tract, and its safety is unquestioned, IP₆ and inositol, its parent compound, holds great promise in our strategies for cancer prevention and therapy [135]. Since phytic acid can only be obtained from plant foods, vegetarians and especially vegans, naturally consume higher levels of phytic acid than meat eaters.

### Fiber

The possible protective association between dietary fiber intake and colorectal cancer was first proposed by Burkitt in 1971 [141]. In addition to the protective benefit of phytic acid, anti-carcinogenic mechanisms of dietary fiber within the bowel include:

i. The formation of short chain fatty acids from fermentation by colonic bacteria,

ii. The reduction of secondary bile acid production,

iii. The reduction in intestinal transit time, and increase of fecal bulk, and

iv. A reduction in insulin resistance [142-144].

Preclinical studies and in vitro studies repeatedly show promise for dietary fiber in the prevention of colon cancer due to its ability to promote the formation of short chain fatty acids from the fermentation of soluble fiber by colonic bacteria, and to inhibit the absorption of bile acids. It is this bile acid binding property that makes fiber a valuable component of the chemopreventive diet. While a significant amount of research has demonstrated the benefits of dietary fiber on colon cancer incidence, this evidence is not straightforward. The types of fiber intake, as well as the amount, has all been associated with reduced colon cancer risk, with a significant amount of research to indicate the likelihood that dietary fiber has a chemoprotective effect on the colon.

Fiber consumption has been linked to a reduced incidence of colon cancer [131]. Vegetarians have lower levels of MMP-2 [116] and their greater intake of foods high in phytic acid may be one reason why.

Another mechanism is by phytic acid forming chelates with various metals and suppressing damaging iron-catalyzed redox reactions. Inasmuch as colonic bacteria have been shown to produce oxygen radicals in appreciable amounts, dietary phytic acid might suppress oxidant damage to intestinal epithelium and neighboring cells [138]. One study sought to determine the potential of phytic acid extracted from rice bran in the suppression of colon carcinogenesis induced by azoxymethane in rats. Phytic acid significantly reduced the number of tumors in the distal, middle and proximal colon [139].

In another study of azoxymethane induced colorectal cancer in rats, the administration of IP₆ markedly suppressed the incidence of tumors when compared to the control. Interestingly, the administration of IP₆ had also markedly decreased β-catenin and COX-2 in colon tumors. Thus, the downregulation of β-catenin and COX-2 could play a role in inhibiting the colorectal cancer development induced by IP₆ and thereby act as a potent anticancer agent [140]. These are elements of rapidly accumulating data from animal models, indicating that dietary supplementation with phytic acid may provide substantial protection against experimentally induced colon cancer.

Should further investigations yield additional support for this hypothesis, purposeful amplification of dietary phytic acid content would represent a simple method for reducing the risk of colon carcinogenesis [138].

Fiber consumption has been linked to a reduced incidence of colon cancer [131]. Vegetarians have lower levels of MMP-2 [116] and their greater intake of foods high in phytic acid may be one reason why.

Another mechanism is by phytic acid forming chelates with various metals and suppressing damaging iron-catalyzed redox reactions. Inasmuch as colonic bacteria have been shown to produce oxygen radicals in appreciable amounts, dietary phytic acid might suppress oxidant damage to intestinal epithelium and neighboring cells [138]. One study sought to determine the potential of phytic acid extracted from rice bran in the suppression of colon carcinogenesis induced by azoxymethane in rats. Phytic acid significantly reduced the number of tumors in the distal, middle and proximal colon [139].

In another study of azoxymethane induced colorectal cancer in rats, the administration of IP₆ markedly suppressed the incidence of tumors when compared to the control. Interestingly, the administration of IP₆ had also markedly decreased β-catenin and COX-2 in colon tumors. Thus, the downregulation of β-catenin and COX-2 could play a role in inhibiting the colorectal cancer development induced by IP₆ and thereby act as a potent anticancer agent [140]. These are elements of rapidly accumulating data from animal models, indicating that dietary supplementation with phytic acid may provide substantial protection against experimentally induced colon cancer. Should further investigations yield additional support for this hypothesis, purposeful amplification of dietary phytic acid content would represent a simple method for reducing the risk of colon carcinogenesis [138].

Preliminary studies in humans show that IP₆ and inositol, the precursor molecule of IP₆, appear to enhance the anticancer effect of conventional chemotherapy, control cancer metastases, and improve quality of life. Because it is efficiently absorbed from the gastrointestinal tract, and its safety is unquestioned, IP₆ and inositol, its parent compound, holds great promise in our strategies for cancer prevention and therapy [135]. Since phytic acid can only be obtained from plant foods, vegetarians and especially vegans, naturally consume higher levels of phytic acid than meat eaters.

### Fiber

The possible protective association between dietary fiber intake and colorectal cancer was first proposed by Burkitt in 1971 [141]. In addition to the protective benefit of phytic acid, anti-carcinogenic mechanisms of dietary fiber within the bowel include:

i. The formation of short chain fatty acids from fermentation by colonic bacteria,

ii. The reduction of secondary bile acid production,

iii. The reduction in intestinal transit time, and increase of fecal bulk, and

iv. A reduction in insulin resistance [142-144].

Preclinical studies and in vitro studies repeatedly show promise for dietary fiber in the prevention of colon cancer due to its ability to promote the formation of short chain fatty acids from the fermentation of soluble fiber by colonic bacteria, and to inhibit the absorption of bile acids. While a significant amount of research has demonstrated the benefits of dietary fiber on colon cancer incidence, this evidence is not straightforward. The types of fiber intake, as well as the amount, has all been associated with reduced colon cancer risk, with a significant amount of research to indicate the likelihood that dietary fiber has a chemoprotective effect on the colon.

Fiber consumption has been linked to a reduced incidence of colon cancer [131]. Vegetarians have lower levels of MMP-2 [116] and their greater intake of foods high in phytic acid may be one reason why.

Another mechanism is by phytic acid forming chelates with various metals and suppressing damaging iron-catalyzed redox reactions. Inasmuch as colonic bacteria have been shown to produce oxygen radicals in appreciable amounts, dietary phytic acid might suppress oxidant damage to intestinal epithelium and neighboring cells [138]. One study sought to determine the potential of phytic acid extracted from rice bran in the suppression of colon carcinogenesis induced by azoxymethane in rats. Phytic acid significantly reduced the number of tumors in the distal, middle and proximal colon [139].

In another study of azoxymethane induced colorectal cancer in rats, the administration of IP₆ markedly suppressed the incidence of tumors when compared to the control. Interestingly, the administration of IP₆ had also markedly decreased β-catenin and COX-2 in colon tumors. Thus, the downregulation of β-catenin and COX-2 could play a role in inhibiting the colorectal cancer development induced by IP₆ and thereby act as a potent anticancer agent [140]. These are elements of rapidly accumulating data from animal models, indicating that dietary supplementation with phytic acid may provide substantial protection against experimentally induced colon cancer. Should further investigations yield additional support for this hypothesis, purposeful amplification of dietary phytic acid content would represent a simple method for reducing the risk of colon carcinogenesis [138].

Preliminary studies in humans show that IP₆ and inositol, the precursor molecule of IP₆, appear to enhance the anticancer effect of conventional chemotherapy, control cancer metastases, and improve quality of life. Because it is efficiently absorbed from the gastrointestinal tract, and its safety is unquestioned, IP₆ and inositol, its parent compound, holds great promise in our strategies for cancer prevention and therapy [135]. Since phytic acid can only be obtained from plant foods, vegetarians and especially vegans, naturally consume higher levels of phytic acid than meat eaters.
The role of fiber is further discussed in the Microbiome section below.

**The Role of the Gut Microbiome**

**Introduction**

Representing a vast ecosystem, the indigenous bacteria in the human gut have various physiological effects and carry out multiple metabolic functions that can influence the health of the human host. Bacteria are thought to benefit the human host in many ways. These favorable effects include:

i. Facilitating the metabolic conversion and uptake of beneficial dietary components;
ii. Producing beneficial fermentation end products that affect intestinal pH and interact with gut mucosa epithelial cells;
iii. Excluding pathogens by competing for attachment sites within the gut mucosa;
iv. Interacting with the intestinal immune system and contributing to the regulation of immune function;
v. Transforming or eliminating toxic substances; and
vi. Generating fecal bulk that decreases transit time and dilutes toxic substances [145].

Carcinogenesis has been associated with the microbiome through direct and indirect routes. Direct pathways include colonization of epithelia by pathogens, or direct interaction with the innate immune system via bacterial antigenic particles with pattern recognition receptors (PRR, e.g. toll-like receptor). Indirect pathways include bacterial production of carcinogens and the production of chemoprotective factors from exogenous sources, such as diet, or from endogenous sources, such as compounds resulting from human metabolism (e.g. bile acids) [146].

An expanding body of evidence supports a role for gut microbes in the etiology of colon cancer. Functional contributions of the gut microbiota that may influence colon cancer susceptibility include:

a. Harvesting otherwise inaccessible nutrients and/or sources of energy from the diet (i.e., fermentation of dietary fibers and resistant starch),
b. Metabolism of xenobiotics, both potentially beneficial and detrimental (i.e., dietary constituents, drugs, carcinogens, etc.),
c. Renewal of gut epithelial cells and maintenance of mucosal integrity, and
d. Affecting immune system development and activity.

Diet and energy balance influence colorectal cancer (CRC) by multiple mechanisms via the gut microbiome. They modulate the composition and function of gut microbiota, which have a prodigious metabolic capacity and can produce oncometabolites or tumor suppressive metabolites depending, in part, on which dietary factors and digestive components are present in the GI tract. Gut microbiota also have a profound effect on immune cells in the lamina propria, which influences inflammation and subsequently CRC.

Nutrient availability, which is an outcome of diet and energy balance, determines the abundance of certain energy metabolites that are essential cofactors for epigenetic enzymes, and therefore impinges upon epigenetic regulation of gene expression. Aberrant epigenetic marks accumulate during CRC, and epimutations that are selected for drive tumorigenesis by causing transcriptome profiles to diverge from the cell of origin. In some instances, the above mechanisms are intertwined, as exemplified by dietary fiber being metabolized by colonic bacteria into butyrate, which is both a short chain fatty acid and a histone deacetylase inhibitor that epigenetically upregulates tumor suppressor genes in CRC cells and anti-inflammatory genes in immune cells [147]. Understanding the complex and dynamic interplay between the gut microbiome, human host immune system, and dietary exposures may help elucidate mechanisms for carcinogenesis and guide future cancer prevention and treatment strategies [146].

**The Role of the Microbiome in the Pathogenesis of Colon Cancer**

The colon flora in meat eaters produce more carcinogens, such as N-Nitroso Compounds (NOC), Hydrogen Sulphide (H2S) and Deoxycholic Acid (DCA), than the flora in vegetarians. Bacteria produce carcinogens by their actions on both exogenous material, such as the production of Nitroso amines from Heme iron, and by their actions on endogenously produced substances, such as bile acids, to produce Deoxycholic acid.

**N-Nitroso compounds (NOC)**

Numerous constituents in red and processed meats may contribute to the increased risk of colon cancer associated with red and processed meat consumption [58]. These include protein and other nitrogenous residues which allow for increased gut bacterial production of N-nitroso compounds (NOC) [148]. Nitrate can be reduced endogenously to nitrite via nitrate reductase produced by the gut bacteria, and nitrite can interact with organic compounds to form NOC. Many classes of NOC have been identified in feces, including nitrosamines, nitrosamides, and nitrosoguanidine [149]. NOC can form DNA adducts which induce mutations. For example, it has been shown that some NOC are alkylation agents that induce GC to AT transitions at the second base of codon 12 or 13 of the K-ras gene-this is a common mutation found in colorectal tumors with K-ras mutations [149].

Diet can influence NOC concentrations. Meat consumption increases the amount of nitrogenous residues in the colon, [150] and in a controlled feeding study in eight men, there was a dose-
response between intake of meat and fecal concentrations of NOC [151]. Fecal water genotoxicity correlated with colonic gene expression changes in pro-carcinogenic pathways, including DNA damage repair, cell cycle, and apoptosis pathways in a 7-day dietary intervention with red meat [152]. Additional controlled feeding studies in men showed that, while heme iron increased fecal NOC, protein sources low in heme (protein from vegetable sources) did not increase fecal NOC [153,154]. The independent effect of heme on NOC suggested that chemical catalysis, in addition to bacterial N-nitrosation, may be responsible for the dose-dependent effect of red meat on increasing endogenous intestinal N-nitrosation [154]. The addition of soy to the diet statistically significantly suppressed fecal NOC [155].

Hydrogen Sulfide (H$_2$S)

Hydrogen sulfide (H$_2$S) is produced by sulfate-reducing bacteria (SRB) and has been shown to have both cytotoxic and genotoxic effects in cell culture studies [156-158]. For example, using a modified comet assay, Attene-Ramos et al. [156] showed that H$_2$S resulted in genomic DNA damage. H$_2$S has also been shown to prevent the oxidation of butyrate by colonic epithelial cells, thereby reducing ATP formation and energy harvest [159]. This lowers the absorption of ions, mucus formation, and cellular detoxification. Roediger et al. [160,161] reported decreased fatty acid oxidation in colonocytes exposed to H$_2$S and there is evidence that sulfide alters cellular redox potential which, in turn, alters cell proliferation [157].

The role of SRB in inflammatory bowel disease and colorectal cancer has been evaluated in several epidemiological and clinical studies [146]. Genomic instability associated with sporadic colon cancer and ulcerative colitis, a risk factor for colon cancer, is thought to result in part from H$_2$S exposure [162]. In a population-based study, the prevalence of SRB was associated with the diets of groups having higher rates of colon cancer [163].

SRB are often members of the normal gut microbiota, and diet can influence their distribution and activity. Dietary protein, especially sulfur-containing amino acids, and inorganic sulfur sources (SO$_4$ in water) contribute to H$_2$S production [164]. In a controlled feeding study, Magee et al. [165] showed that H$_2$S was significantly related to the amount of meat protein consumed.

Dietary fat

Cani et al. [166] found that a high fat diet resulted in a significant change in the composition of the dominant bacterial populations within the gut microflora, including a decrease in the number of Bifidobacteria, Eubacterium, rectal Clostridium cocoides group, and Bacteroides, thus favoring an increase in the gram-negative to gram-positive ratio. This change in gut microflora composition was associated with a significant increase in plasma lipopolysaccharide (LPS) levels, fat mass, body weight gain, liver hepatic triglyceride accumulation, insulin resistance, and diabetes [166,167]. In addition, de Wit et al. [168] observed that a high saturated fatty acid diet enhanced an overflow of dietary fat to the distal intestine, which affected the gut microbiota composition.

Lipopolysaccharide (LPS, also known as endotoxin) is a bacterial cell wall component in gram-negative bacteria that is associated with low grade, chronic inflammation in obesity [166,169,170] and colorectal cancer [171] LPS acts through toll-like receptor-4 (TLR-4), a PRR associated with innate immunity, which triggers TGF-β-mediated pathways [172,173]. This leads to the expression of various genes that promote neoplasia, including those of growth factors and inflammatory mediators. Serum LPS binding protein (LBP), [174,175] a protein that binds LPS upon activation of TLR-4, is correlated with circulating concentrations of LPS, and a recent prospective study showed that polymorphisms in the LBP gene were associated with increased colorectal cancer risk [176].

Deoxycholic acid (DCA)

The secondary bile acid, deoxycholic acid (DCA), a colonic bacterial transformation product, has been implicated in gallstone formation and colorectal carcinogenesis [177,178]. Serum DCA levels, which may reflect the bile acid pool more accurately, also have been shown to be higher in patients with colon cancer than in healthy individuals [179,180]. Vegetarian diets result in significantly lower levels of DCA than the standard American diet [181,182]. A proposed mechanism for associations between DCA and colon cancer is that DCA may change the balance between apoptosis, proliferation, and differentiation in the intestinal epithelium [183], acting through interference of tumor suppression and enhancing stimulation of growth via cell signaling pathways. In addition, the higher fiber intake of the vegetarian diet results in increased fecal bulk, thus lessening the concentration of DCA in the colon. The more rapid transit time that results from a high fiber diet further reduces exposure to DCA [184,185].

How the microbiome can prevent colon cancer

Among the dietary factors, several plant-derived compounds have been found to afford colon cancer protection. These compounds influence many 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.

Butyrate

The gut microbiota can ferment complex dietary residues that are resistant to digestion by enteric enzymes. This process provides energy for the microbiota and culminates in the release of short chain fatty acids including butyrate, propionate and acetate. Propionate and acetate are beneficial in lowering the pH...
of the stool, whereas butyrate is utilized for the metabolic needs of the colon and the body. Butyrate has a remarkable array of colonic health promoting and antineoplastic properties: it is the preferred energy source for colonocytes, it maintains mucosal integrity, and it suppresses inflammation and carcinogenesis through effects on immunity, gene expression and epigenetic modulation [186].

**Polyphenols**

Plant-derived polyphenols are active mediators of cellular events, targeting key carcinogenic pathways, and modulating colonic microbial populations. In turn, the colonic microbiota metabolize dietary compounds and mediate cellular events. Hence, dietary bioactive compounds and the intestinal microbiota create a complex milieu that directly affects the carcinogenic events of the colon [187]. Consumption of cruciferous or Brassica vegetables has been shown to be inversely associated with risk of some cancers [188]. Glucosinolates are converted into isothiocyanates (ITCs) by bacterially produced thioglucosidases. Previous studies have shown that certain species of bacteria, such as *Escherichia coli*, *Bacteroides thetaiotaomicron*, *Enterococcus faecalis*, *E. faecium*, *Peptostreptococcus sp.*, and *Bifidobacterium sp.*, isolated from the human gut or feces, can convert glucosinolates into ITC and other derivatives [189-191].

Isothiocyanates (ITCs) have been shown to have anti-carcinogenic properties both in vitro and in vivo [192]. The biologic effects of ITCs are diverse, including interaction with multiple signaling pathways important to carcinogenesis as well as cross talk between pathways. As explained in the section on Sulforaphane (an example of ITC), the inhibitory activity of ITCs against tumorigenesis is inferred by its ability to modulate Phase 1 and 2 biotransformation enzyme activities, thereby affecting several processes related to chemical carcinogenesis, such as the metabolism and DNA binding of carcinogens. In vivo studies have also indicated that ITCs induce apoptosis [193].

**Fiber**

Dietary fiber appears critical in influencing the composition and metabolic activity of the microbiome, determining levels of short chain fatty acids important for intestinal health. Western style diets, high in fat and sugar, and low in fiber decrease beneficial Firmicutes that metabolize dietary-fiber-derived polysaccharides to short chain fatty acids [194]. However, in healthy individuals, fiber intake improves the gut microbiota [195].

Dietary fiber of edible plants comprises insoluble and soluble carbohydrates including cellulose, lignin, and nonstarch polysaccharides such as hemicelluloses, pectins and arabinoxylan oligosaccharides [194,196]. Other dietary fiber components include nondigestible oligosaccharides such as inulin and oligofructose, as well as resistant starch [194,196,197]. They demonstrate resistance to digestion in the human small intestine, allowing passage largely intact into the colon where they increase viscosity and bulking of the fecal matter [198]. Importantly, it is here that dietary fiber undergoes fermentation by the resident colonic microbiota to short chain fatty acids (primarily butyrate, acetate and propionate) that act as the primary carbon energy source for colonocytes [199-201]. In particular, butyrate has been reported to be protective against development of colitis [202] and colorectal cancer [203,204].

**The Vegan Advantage**

When vegan diets are directly compared to vegetarian and omnivorous diets, a pattern of protective health benefits emerges. The relatively recent inclusion of vegan diets in studies of gut microbiota and health allows us the opportunity to assess whether the vegan gut microbiota is distinct, and whether the many health advantages characteristic of a vegan diet may be partially explained by the associated microbiota profile. The relationship between diet and the intestinal microbial profile appears to follow a continuum, with vegans displaying a gut microbiota most distinct from that of omnivores [205]. The vegan gut profile appears to be unique in several characteristics, including a reduced abundance of pathogens and a greater abundance of protective species. Reduced levels of inflammation may be the key feature linking the vegan gut microbiota with protective health effects [205]. Vegans have a higher ratio than meat eaters of Faecalibacterium prausnitzii, an anti-inflammatory bacterium and abundant butyrate producer in the class Clostridia (phylum Firmicutes), purported to play a protective role for colonocytes [205].

A recent, large-scale study by Zimmer et al. [206] set out to distinguish the fecal microbiota profile of vegans from that of vegetarians, and from an equal number of controls consuming an omnivorous diet. Vegan and vegetarian subjects had adhered to their proclaimed diet for at least 4 weeks prior to the study. Vegan samples had significantly lower microbial counts than their omnivore counterparts for four bacterial taxa: Bacteroides, Bifidobacterium, *E. coli* and Enterobacteriaceae. Interestingly, the vegetarian sample also showed significantly reduced Bacteroides and Bifidobacteria, a result found 37 years earlier by Reddy [181]. In a small Indian study, the dominant phylum from healthy vegetarians was found to be Firmicutes (34%), followed by Bacteroidetes (15%). The balance was reversed in non-vegetarian (Bacteroidetes 84%, Firmicutes 4%). The colon cancer and IBD patients had higher percentages of Bacteroidetes (55% in both) than Firmicutes (26% and 12%, respectively) than the healthy non-vegetarian [207]. This difference may help account for the lower risk vegetarians have of colon cancer.

**Secondary Prevention**

While there are currently no studies on the effect of an overall vegetarian diet on those who already have colon cancer, recurrence studies have shown a substantially raised risk of recurrence of colon cancer for those consuming processed
meat. However, those consuming plant foods such as legumes and tree nuts had the risk of recurrence lowered. The studies on recurrence that are available are detailed below. This field warrants further study. Disease-free survival among colorectal cancer patients was significantly worsened among patients with a high processed meat dietary pattern raising the risk of recurrence by 85% [208]. However, certain plant foods, in particular beans, cereals and nuts, have been shown to be especially efficacious in preventing colon cancer recurrence. Those colon cancer patients who are in the highest quartile of bean consumption reduced the risk of advanced adenomas recurrence by 65%. Those in the highest quartile of peas and green beans consumption reduced the risk of advanced adenoma recurrence by 49% [209].

In a recent prospective study involving 1575 patients with Stage I to III colorectal cancer, high fiber intake especially from cereals was associated with a low colorectal-cancer-specific mortality and overall mortality [210]. In the past few years, an inverse correlation between nut consumption and major chronic diseases such as cardiovascular diseases, metabolic syndrome, and type 2 diabetes has been established [211-215]. In addition, studies have suggested that nut consumption could also have a chemo preventive effect, especially on colorectal and prostate cancer [216,217]. Recent epidemiological studies have confirmed an inverse association between frequent nut consumption and cancer mortality [218-220].

An observational study of 826 patients with stage III colon cancer showed that those who consumed two ounces or more of tree nuts per week had a 42% lower chance of cancer recurrence and 57% lower chance of death than those who did not eat nuts [221]. Nuts contain many bioactive compounds that have been found to affect several cellular processes involved in tumor development and progression, including cell survival, cell proliferation, cell invasion, and angiogenesis [222,223] and therefore can account for the anticancer properties of nuts.

**Clinical Considerations**

The benefits of a plant-based diet in reducing the risk of colon cancer, and in preventing recurrence, should be explained to every patient, and they can be presented with the option to change their diet. A quality of life study found that colorectal patients following a "Western" meat centered diet had a 45% lower chance to improve in physical functioning, 30% lower chance to improve constipation and a 44% lower chance to improve diarrhea over time compared to patients following a fruit and vegetable diet who also reported a better quality of life [224]. These are symptoms that no patient would wish to prolong. The plant-based diet has the distinct advantage of having no contraindications or adverse reactions. Since age is a major risk factor for colon cancer, many colon cancer patients are also at higher risk of coronary artery disease and Type 2 Diabetes. The plant-based diet is both safe and efficacious for these comorbidities as well [225,226].

When treating patients with a plant-based diet, physicians should also monitor those patients with such comorbidities, and be careful not to underestimate the efficacy of a plant-based to treat these common comorbidities. For instance, the plant-based diet can lower glycosylated Hb significantly more than the frontline drug, Metformin [227,228] and is as efficacious for the treatment of treatment of hypercholesterolemia as the reductase inhibitor, Lovostatin [229]. Therefore, medications should be titrated as the treatment effects for comorbidities become evident.

**Discussion**

The WHO and the ACIR have classified processed meats as a group 1 carcinogen based on the strength of evidence. This is the same category as tobacco. While tobacco probably has an even greater deleterious effect on overall public health, the potential negative impact of consuming processed meats should be explained to all patients. They should also be informed that red meat is in group 2A as a probable carcinogen. The plant-based diet very significantly treats several risk factors for colon cancer while reducing the risk of colon cancer itself. We now know of several mechanisms by which this occurs. This should increase the confidence of physicians when prescribing a plant-based diet for the primary prevention of colon cancer.

Currently, the prevention of colon cancer is carried out by the widespread use of fecal testing, colonoscopies and tomography followed by polypectomy. But colonoscopy, with excision of a pedunculated or sessile polyp, is really secondary prevention and it comes at quite a price tag for the country. According to a New York Times article, the price tag for colonoscopies averages $1,185 and is often much, much more — as much as $4,090 in the Twin Cities, according to Healthcare Blue Book data. That’s less than New York City’s $8,517, but much more than Baltimore’s $1,908. Data from the Centers for Disease Control and Prevention suggests that more than 10 million people have a colonoscopy each year, adding up to more than $10 billion in annual costs. Also, let’s not forget that the procedure is not risk free and is unpleasant for the patient at best. About one in three adults aged 50 to 75 years have not been tested for colorectal cancer as recommended by the United States Preventive Services Task Force. This may be due in part to the expense and the discomfort anticipated by the patients about the procedure.

With all these disadvantages, the question that naturally comes to mind is what can the patient be offered for primary prevention? Evidence shows that a plant-based diet is both safe and efficacious for the primary prevention of colon cancer. The advantage of at least a 50% reduction in colon cancer risk is too significant to be overlooked, especially for one of the more common malignant pathologies. Diet is also a significant factor in reducing colon cancer recurrence.
References

1. Anand P, Kunnunukara A, Sundamn C, Hari Kumar K, Tharakaran S, et al. (2008) Cancer is a Preventable Disease that Requires Major Lifestyle Changes. Pharm Res 25(9): 2097-2116.

2. Singh P, Fraser G (1998) Dietary risk factors for colon cancer in a low-risk population. Am J Epidemiol 148(9): 761-774.

3. Bingham SA (2000) Diet and colorectal cancer prevention. Biochem Soc Trans 28(2): 12-16.

4. Willett WC (1995) Diet, nutrition, and avoidable cancer. Environ Health Perspect 8: 165-170.

5. Bouter N, Wilpert M, Faire J (1991) Diet and colorectal cancer. Eur J Cancer Prev 2: 13-20.

6. Potter JD (1996) Nutrition and Colorectal Cancer. Cancer Causes Control 7(1): 127-146.

7. Chen Z, Wang P, Woodward J, Zhu Y, Roebotan B, et al. (2015) Dietary patterns and colorectal cancer: results from a Canadian population-based study. Nutr J 14: 18.

8. World Cancer Research Fund / American Institute for Cancer Research (2007) Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective. AICR, Washington DC, USA.

9. Lanou A, Svensson B (2011) Reduced cancer risk in vegetarians: an analysis of vegetarians. Cancer Manag Res 3: 1-8.

10. Tabung F, Brown L, Fung T (2018) Dietary patterns and colorectal cancer risk: a review of 17 years of evidence (2000–2016). Curr Colorectal Cancer Rep 13(6): 440-454.

11. Schwingshackl L, Schwedhelm C, Hoffmann G, Knüppel S, Laure Preterre A, et al. (2018) Food groups and risk of colorectal cancer. Int J Cancer 142(9): 1748-1758.

12. Andaloussi T, Lukanova A, Ferrari P, Riboli E (2002) Meat consumption and colorectal cancer risk: a meta-analytical approach. Cancer Epidemiol Biomarkers Prev 10(5): 439-446.

13. Larsson S, Wolk A (2006) Meat consumption and risk of colorectal cancer: a meta-analysis of prospective studies. Int J Cancer 119(11): 2657-2664.

14. Orlich M, Sabate J, Fan J, Svenn L, et al. (2015) Vegetarian dietary patterns and the risk of colorectal cancers. JAMA Intern Med 175(5): 767-776.

15. Brouvard V, Loomis D, Goyton K, Grosse Y, Ghissassi F, et al. (2015) Carcinogenicity of consumption of red and processed meat. Lancet Oncol 16(16): 1599-600.

16. Domingo J, Nadal M (2017) Carcinogenicity of consumption of red meat and processed meat: A review of scientific news since the IARC decision. Food Chem Toxicol 105: 256-261.

17. Kaaks R, Lukanova A (2001) Energy balance and cancer: the role of insulin and insulin-like growth factor-I. Proc Nutr Soc 60(1): 91-106.

18. Rizzo N, Sabaté J, Jaceldo-Siegl K, Fraser G (2017) Vegetarian dietary patterns are associated with a lower risk of metabolic syndrome: the adventist health study 2. Diabetes Care 34(5): 1225-1227.

19. Vařačková M, Krajčevcová-Kudláčková M, Blazíček P, Babičková K (2006) No evidence of insulin resistance in normal-weight vegetarians: A case control study. Eur J Nutr 45(1): 52-54.

20. Kuo C, Lai N, Ho L, Lin C (2004) Insulin sensitivity in Chinese ovo-lacto-vegetarians compared with omnivores. Eur J Clin Nutr 58(2): 312-316.

21. Ma Y, Yang Y, Wang P, Zhang P, Shi C, et al. (2013) Obesity and Risk of colorectal Cancer: A Systematic Review of Prospective Studies. PLoS One 8(1): e53916.

22. Tonstad S, Butler T, Yan R, Fraser G (2009) Type of Vegetarian Diet, Body Weight, and Prevalence of Type 2 Diabetes. Diabetes Care 33(5): 791-796.

23. Bradbury K, Crowe F, Appleby P, Schmidt J, Travis R, et al. (2014) Serum concentrations of cholesterol, apolipoprotein A-I, and apolipoprotein B in a total of 1694 meat-eaters, fish-eaters, vegetarians, and vegans. Eur J Clin Nutr 68(2): 170-183.

24. Waldmann A, Koschzike J, Leitzmann C, Hahn A (2005) German vegan study: diet, lifestyle factors, and cardiovascular risk profile. Ann Nutr Metab 49(6): 366-372.

25. Haddad E, Tanzman M (2003) What do vegetarians in the United States eat? Am J Clin Nutr 78(3): 626S-632S.

26. Newby P, Tucker K, Wolk A (2005) Risk of overweight and obesity among semi-vegetarian, lacto-vegetarian, and vegan women. Am J Clin Nutr 81(6): 1267-1274.

27. Freeman H (2008) Colorectal cancer risk in Crohn’s disease. World J Gastroenterol 14(12): 1810-1811.

28. D’Souza S, Levy E, Mack D, Israel D, Lambrette P, et al. (2008) Dietary patterns and risk for Crohn’s disease in children. Inflamm Bowel Dis 14(3): 367-373.

29. Lj Y, Niu Y, Sun X, Zhang F, Liu G, et al. (2015) Role of phytochemicals in colorectal cancer prevention. World J Gastroenterol 21(31): 9262-9272.

30. Spencer JP, Crozier A, eds. (2012) Flavonoids and Related Compounds. Boca Raton, CRC Press, Taylor & Francis Group.

31. Baron JA (2003) Epidemiology of non-steroidal anti-inflammatory drugs and cancer. Prog Exp Tumor Res 37: 1-24.

32. Elwood P, Gallagher A, Duthie G, Mur LA, Morgan G (2009) Aspirin, salicylates, and cancer. Lancet. 373(9671): 1301-1309.

33. Sandler R, Halabi S, Baron J, Budinger S, Paskett E, et al. (2003) A randomized trial of aspirin to prevent colorectal adenomas in patients with previous colorectal cancer. N Engl J Med 348(10): 883-890.

34. Chan A, Ogino S, Fuks C (2009) Aspirin use and survival after diagnosis of colorectal cancer. JAMA 302(6): 649-658.

35. Jacobs E, Thun M, Bain E, Rodriguez C, Henley SJ, et al. (2007) A large cohort study of long-term daily use of adult-strength aspirin and cancer incidence. J Natl Cancer Inst 99(8): 608-615.
Cancer Therapy & Oncology International Journal

42. Din F, Theodoratou E, Farrington S, Tenesa A, Barnetson RA, et al. (2010) Effect of aspirin and NSAIDs on risk and survival from colorectal cancer. Gut 59(12): 1670-1679.

43. Holmes M, Chen W, Li L, Hertzmark E, Spiegelman D, et al. (2010) Aspirin intake and survival after breast cancer. J Clin Oncol 28(9): 1467-1472.

44. Juárez Olguín H, Flores Pérez J, Lares Asself I, Loredo Abdala A, Carballo Rodríguez L, et al. (2004) Comparative pharmacokinetics of acetyl salicylic acid and its metabolites in children suffering from autoimmune diseases. Biopharm Drug Dispos 25(1): 1-7.

45. Duthie G, Wood A (2011) Natural salicylates: Foods, functions and disease prevention. Food Funct 2(9): 515-520.

46. Paterson J, Baxter GL, Lawrence J, Duthie G (2006) Is there a role for dietary salicylates in health? Proc Nutr Soc 65(1): 93-96.

47. Jansen M, Bueno-de-Mesquita H, Buzina R, Fidanza F, Menotti A, et al. (1999) Dietary fiber and plant foods in relation to colorectal cancer mortality: The Seven Countries Study. Int J Cancer 82(1): 174-179.

48. Howe G, Benito E, Castello R, Cormeé J, Estève J, et al. (1992) Dietary Intake of Fiber and Decreased Risk of Cancers of the Colon and Rectum: Evidence From the Combined Analysis of 13 Case-Control Studies. J Natl Cancer Inst 84(24): 1887-1896.

49. Peters U, Sinha R, Chatterjee N, Subar A, Ziegler R, et al. (2003) Dietary fibre and colorectal adenoma in a colorectal cancer early detection program. Lance 361(9368): 1491-1495.

50. Nomura A, Hankin J, Henderson B, Wilkins L, Murphy S, et al. (2007) Dietary fiber and colorectal cancer risk: the multiethnic cohort study. Cancer Causes Control 18(7): 753-764.

51. Wakai K, Date C, Fukui M, Tamakoshi K, Watanabe Y, et al. (2007) Dietary Fiber and Risk of Colorectal Cancer in the Japan Collaborative Cohort Study. Cancer Epidemiol Biomarkers Prev 16(4): 668-675.

52. Dahm C, Keogh R, Spencer E, Greenwood D, Key T, et al. (2010) Dietary Fiber and Colorectal Cancer Risk: A Nested Case-Control Study Using Food Diaries. J Natl Cancer Inst 102(9): 614-626.

53. McClar M, Harnack L, Limburg P, Anderson F, Kolsom A (2006) Incidence of colorectal cancer in relation to glycemic index and load in a cohort of women. Cancer Epidemiol Biomarkers Prev 15(5): 892-896.

54. Bingham S, Norat T, Moskal A, Ferrari P, Slimani N, et al. (2005) Is the Association with Fiber from Foods in Colorectal Cancer Confounded by Fiber Intake? Cancer Epidemiol Biomarkers Prev 14(6): 1552-1556.

55. Murphy N, Norat T, Ferrari P, Jenab M, Bueno-de-Mesquita B, et al. (2012) Dietary Fibre Intake and Risks of Colon and Rectum in the European Prospective Investigation into Cancer and Nutrition (EPIC). PLoS One. 7(6): e39361.

56. World Cancer Research Fund / American Institute for Cancer Research (2011) Continuous Update Project Report Summary. Food, Nutrition, Physical Activity, and the Prevention of Colorectal Cancer: AICR, Washington DC, USA.

57. Cross A, Ferrucci L, Rich A, Graubard B, Ward M, et al. (2010) A large prospective study of meat consumption and colorectal cancer risk: an investigation of potential mechanisms underlying this association. Cancer Res 70(6): 2406-2414.

58. Bastide N, Pierre F, Corpet D (2011) Heme iron from meat and risk of colorectal cancer: a meta-analysis and a review of the mechanisms involved. Cancer Prev Res (Phila) 4(2): 177-184.

59. Zheng W, Lee S (2009) Well-done meat intake, heterocyclic amine exposure, and cancer risk. Nutr Cancer 61(4): 437-446.

60. Sinha R, Peters U, Cross A, Kuldorff M, Weissfeld J, et al. (2005) Meat, meat cooking methods and preservation, and risk for colorectal adenoma. Cancer Res 65(17): 8034-8041.

61. Ward M, Cross A, D’Avino H, Kuldorff M, Nowell-Kadlubar S, et al. (2007) Processed meat intake, CYP2A6 activity and risk of colorectal adenoma. Carcinogenesis 28(6): 1210-1216.

62. Hossam M, Grimalt J, Guinó E, Navarro M, Martí-Ragué J, et al. (2004) Organochlorine Exposure and Colorectal Cancer Risk. Environ Health Perspect 112(15): 1460-1466.

63. Miller P, Lazurus P, Lesko S, Cross AJ, Sinha R, et al. (2013) Meat-Related Compounds and Colorectal Cancer Risk by Anatomical Subsite. Nutr Cancer 65(2): 202-226.

64. Turteltaub K, Dingley K, Curtis K, Malfatti M, Turesky R, et al. (1999) Macromolecular adduct formation and metabolism of heterocyclic amines in humans and rodents at low doses. Cancer Lett 143(2): 149-155.

65. Cross A, Sinha R (2004) Meat-related mutagens/carcinogens in the etiology of colorectal cancer. Environ Mol Mutagen 44(1): 44-55.

66. Gunter M, Divi R, Kulloff M, Vermeulen R, Haverkos H, et al. (2007) Leukocyte polycyclic aromatic hydrocarbon-DNA adduct formation and colorectal adenoma. Carcinogenesis 28(7): 1426-1429.

67. Peters U, DeMarini D, Sinha R, Brooks L, Warren S, et al. (2003) Urinary mutagenicity and colorectal adenoma risk. Cancer Epidemiol Biomarkers Prev 12(11 Pt 1): 1253-1256.

68. Shin A, Shrubsole M, Rice J, Cai Q, Doll M, et al. (2008) Meat intake, heterocyclic amine exposure, and metabolizing enzyme polymorphisms in relation to colorectal polyp risk. Cancer Epidemiol Biomarkers Prev 17(2): 320-329.

69. Kampman E, Slattery M, Bigler J, Leppert M, Samowitz W, et al. (1999) Meat consumption, genetic susceptibility, and colon cancer risk: a United States multicenter case-control study. Cancer Epidemiol Biomarkers Prev 8(1): 15-24.

70. Le Marchand L, Hankin J, Pierce L, Sinha R, Nerurkar P, et al. (2002) Well-done red meat, metabolic phenotypes and colorectal cancer in Hawaii. Mutat Res 506-507: 205-214.

71. Nomura A, Hankin J, Levin B, Meyskens F, Doll R, et al. (2006) Analysis of total meat intake and exposure to individual heterocyclic amines in a case-control study of colorectal cancer: contribution of metabolic variation to risk. Mutat Res 506-507: 175-185.

72. Butler L, Millikan R, Sinha R, Keku T, Winkel S, et al. (2008) Modification by N-acetyltransferase 1 genotype on the association between dietary heterocyclic amines and colon cancer in a multiethnic study. Mutat Res 638(1-2): 162-174.

73. Chen J, Stampfer M, Hough H, Garcia-Closas M, Willett W, et al. (1998) A prospective study of N-acetyltransferase genotype, red meat intake, and risk of colorectal cancer. Cancer Res 58(15): 3307-3311.

74. Joshi A, Corral R, Siegmund K, Haile R, Le Marchand L, et al. (2009) Red meat and poultry intake, polymorphisms in the nucleotide excision repair and mismatch repair pathways and colorectal cancer risk. Carcinogenesis 30(3): 472-479.

75. Lang N, Butler M, Massengill J, Lawson M, Stotts R, et al. (1994) Rapid metabolic phenotypes for acetyltransferase and cytochrome P450A12 and putative exposure to food-borne heterocyclic amines increase the risk for colorectal cancer or polyps. Cancer Epidemiol Biomarkers Prev 3(8): 675-682.

76. Le Marchand L, Hankin J, Wilkens L, Pierce L, Franke A, et al. (2001) Combined effects of well-done red meat, smoking, and rapid N-acetyltransferase 2 and CYP1A2 phenotypes in increasing colorectal cancer risk. Cancer Epidemiol Biomarkers Prev 10(12): 1259-1266.

77. Probst-Hensch N, Haile R, Ingles S, Longnecker M, Han C, et al. (1995) Acetylation polymorphism and prevalence of colorectal adenomas. Cancer Res 55(10): 2017-2020.
Cancer Therapy & Oncology International Journal

78. Roberts-Thomson I, Ryan P, Khoo K, Hart W, McMichael A, et al. (1996) Diet, acetylator phenotype, and risk of colorectal neoplasia. Lancet 347(9012): 1372-1374.

79. Chan A, Tranah G, Giovannucci E, Willett W, Hunter D, et al. (2005) Prospective study of N-acetyltransferase-2 genotypes, meat intake, smoking and risk of colorectal cancer. Int J Cancer 115(4): 648-652.

80. Phillips DH (1999) Polycyclic aromatic hydrocarbons in the diet. Mutat Res 443(1-2): 129-147.

81. Buckley T, Lisy P (1992) An examination of the time course from human dietary exposure to polycyclic aromatic hydrocarbons to urinary elimination of 1-hydroxypyrene. Br J Ind Med 49(2): 113-124.

82. Hamidi E, Hajeb S, Selamat A, Abdul Razis A (2016) Polycyclic Aromatic Hydrocarbons (PAHs) and their Bioaccessibility in Meat: a Tool for Assessing Human Cancer. Asian Pac J Cancer Prev 17(1): 15-23.

83. Goldman R, Shields P (2003) Food Mutagens. J Nutr 133(3): 965S-973S.

84. Probst-Hensch N, Sinha R, Longnecker M, Witte J, Ingles S, et al. (1997) Meat preparation and colorectal adenomas in a large case-control study in California (United States). Cancer Causes Control 8(2): 175-183.

85. Giovannucci E, Rimm E, Stampfer M, Colditz G, Ascherio A, et al. (1994) Intake of fat, meat, and fiber in relation to risk of colon cancer in men. Cancer Res 54(9): 2390-2397.

86. Santoncini S, Albrizio S, Murr U, Ferrante M, Mercogliano R (2017) Study on the occurrence of polycyclic aromatic hydrocarbons in milk and meat/fish-based baby food available in Italy. Chemosphere 184: 467-472.

87. Tricker A, Preussmann R (1991) Carcinogenic N-nitrosamines in the diet: occurrence, formation, mechanisms and carcinogenic potential. Mutat Res 259(3-4): 277-289.

88. Fishier B (1999) Most Unwanted. Environ Health Perspect 107(1): A18-A23.

89. Dougherty C, Henricks S, Reinert J, Panayocott L, Axeldad D, et al. (2000) Dietary exposures to food contaminants across the United States. Environ Res 84(2): 170-185.

90. Kiviranta H, Tsuchimoto J, Tuokkaiten J, Vartiaieta T (2005) Polychlorinated dibenzo-p-dioxins, dibenzofurans, and biphenyls in the general population in Finland. Chemosphere 60(7): 854-869.

91. Kopp T, Vogel U, Tonnemand A, Andersen V (2018) Meat and fiber intake and interaction with pattern recognition receptors (TLR1, TLR2, TLR4, and TLR10) in relation to colorectal cancer in a Danish prospective, case-cohort study. Am J Clin Nutr 107(3): 465-479.

92. Arcidiacano B, Iritano S, Nocera A, Possidente K, Nevolo M, et al. (2012) Insulin Resistance and Cancer Risk: An Overview of the Pathogenic Mechanisms. Exp Diabetes Res 2012: 789174.

93. Giovannucci E (1995) Insulin and Colon Cancer. Cancer Causes Control 6(2): 164-179.

94. Pollak M (2008) Insulin and insulin-like growth factor signalling in neoplasia. Nature Reviews Cancer 8(12): 915-928.

95. Frasca F, Pandini G, Sciacca L, Mineo R, et al. (1999) Insulin receptor isoform A, a newly recognized, high-affinity insulin-like growth factor II receptor in fetal and cancer cells. Mol Cell Biol 19(5): 3278-3288.

96. Vigneri P, Frasca F, Sciacca L, Pandini G, Vigneri R (2009) Diabetes and cancer. Endocr Relat Cancer 16(4): 1103-1123.

97. Nakae J, Kido Y, Acchi D (2001) Distinct and overlapping functions of insulin and IGF-I receptors. Endocr Rev 22(6): 818-835.

98. Siddle K (2011) Signalling by insulin and IGF receptors: supporting acts and new players. J Mol Endocrinol 47(1): R1-10.

99. Mostafal S, Grako K, Dull T, Coussens L, Ulrich E, et al. (1990) Functionally distinct insulin receptors generated by tissue-specific alternative splicing. EMBO J 9(8): 2409-2413.

100. Comstock S, Xu D, Hertog K, Kouvou B, McCasky S, et al. (2014) Association of insulin-related serum factors with colorectal polyp number and type in adult males. Cancer Epidemiol Biomarkers Prev 23(9): 1843-1851.

101. Yoshida I, Suzuki A, Vallaee M, Matano Y, Masunaga T, et al. (2006) Serum insulin levels and the prevalence of adenomatous and hyperplastic polyps in the proximal colon. Clin Gastroenterol Hepatol 4(10): 1225-1231.

102. Lahm H, Amstad P, Wyniger J, Yilmaz A, Fischer J, et al. (1994) Blockade of the insulin-like growth-factor-I receptor inhibits growth of human colorectal cancer cells: evidence of a functional IGF-II-mediated autocrine loop. Int J Cancer 50(3): 452-459.

103. Bowers L, Rossi E, O’Flanagan D, deGrafenried L, Hursting S (2015) The role of the insulin/IGF system in cancer: lessons learned from clinical trials and the energy balance-cancer link. Front Endocrinol (Lausanne) 6: 77.

104. Frasca F, Pandini G, Sciacca L, Pezzino V, Squatrito S, et al. (2008) The role of insulin receptors and IGF-I receptors in cancer and other diseases. Arch Physiol Biochem 114(1-4): 23-37.

105. Stojasvilevic S, Virovic J, Kular J, Duvnjak M (2016) The relationship between insulin resistance and colon cancer. Endocr Oncol Metab, p. 24-33.

106. Giovannucci E (2001) Insulin, insulin-like growth factors and colon cancer: a review of the evidence. J Nutr. 131(11 Suppl): 3109S-20S.

107. Allen N, Appleby P, Davey G, Kaaks R, Rinaldi S, et al. (2002) The associations of diet with serum insulin-like growth factor I and its main binding proteins in 292 women meat-eaters, vegetarians, and vegans. Cancer Epidemiol Biomarkers Prev 11(11): 1441-1448.

108. Allen N, Appleby P, Davey G, Key T (2000) Hormones and diet: low insulin-like growth factor-I but normal bioavailable androgens in vegan men. Br J Cancer 83(1): 95-97.

109. Kersten C, Lohimo J, Algars A, Lahdesmaki A, Cvancerova M, et al. (2013) Increased C-reactive protein implies a poorer stage-specific prognosis in colon cancer. Acta Oncologica (Stockholm, Sweden) 52(8): 1691-1698.

110. Kigawa N, Budhathoki S, Yamaji, T, Iwasaki M, Inoue M, et al. (2017) Association of plasma C-reactive protein level with the prevalence of colorectal adenoma: the Colorectal Adenoma Study in Tokyo. Sci Rep 7(1): 4456.

111. Davenport J, Cai Q, Ness R, Milne G, Zhao Z, et al. (2016) Evaluation of Pro-inflammatory Markers Plasma C-reactive Protein and Urinary Prostaglandin-E2 Metabolite in Colorectal Adenoma Risk. Mol Carcinogenesis. 55(6): 1251-1261.

112. Ananthakrishnan A, Cheng S, Cai T, Cagan A, Gainer V, et al. (2014) Serum Inflammatory Markers and Risk of Colorectal Cancer in Patients with Inflammatory Bowel Diseases. Clin Gastroenterol Hepatol 12(8): 1342-1348.

113. Szeto Y, Kwok T, Benzzi I (2004) Effects of long-term vegetarian diet on biomarkers of antioxidant status and cardiovascular disease risk. Nutr 20(10): 863-866.

114. Haghhiatdost F, Bellissimo N, Totosy de Zepetnek J, Rouhani M (2016) The role of inflammation in cancer prevention with a Plant-Based Diet. Canc Therapy & Oncol Int J. 2019; 15(2): 555906. DOI: 10.19080/CTOIJ.2019.15.555906
116. Navarro J, de Gouveia L, Rocha-Penha L, Cinegaglia N, Belo V, et al. (2016) Reduced levels of potential circulating biomarkers of cardiovascular diseases in apparently healthy vegetarian men. Clinica Chimica Acta 461: 110-113.

117. Zucker S, Vacirca J (2004) Role of matrix metalloproteinases (MMPs) in colorectal cancer. Cancer Metastasis Rev 23(1-2): 101-117.

118. Matusheski N, Juvik J, Jeffery F (2004) Heating decreases epithelial protein activity and increases sulforaphane formation in broccoli. Phytochemistry 65(9): 1273-1281.

119. Cooper D, Webb D, JC P (1997) Evaluation of the potential for oles to affect the availability of dietary phytochemicals. J Nutr 127(8 Suppl): 1699S-1709S.

120. Winiwarter S, Bonham N, Ax F, Hallberg A, Lennernäs H, et al. (1998) Correlation of human jejunal permeability (in vivo) of drugs with experimentally and theoretically derived parameters. A multivariate data analysis approach. J Med Chem 41(25): 4939-4949.

121. Zhang Y, Callaway E (2002) High cellular accumulation of sulforaphane, a dietary anticarcinogen, is followed by rapid transporter-mediated export as a glutathione conjugate. Biochem J 364(Pt 1): 301-307.

122. Kassahun K, Davis M, Hu P, Martin B, Ballie T (1997) Biotransformation of the naturally occurring isothiocyanate sulforaphane in the rat: identification of phase I metabolites and glutathione conjugates. Chem res toxicol 10(11):1228-1233.

123. Tomczyk J, Olejnik A (2010) Sulforaphane—a possible agent in prevention and therapy of cancer. Postepy Hig Med Dosw (online) 64: 590-603.

124. Zeng H, Trujillo O, Moyer M, Botnen J (2011) Prolonged sulforaphane treatment activates survival signaling in nontumorigenic NCM460 colon cells but apoptotic signaling in tumorigenic HCT116 colon cells. Nutr Cancer 63(2): 248-255.

125. Gamet-Payrastre L, Li P, Lumeau S, Cassar G, Dupont M, et al. (2000) Sulforaphane, a naturally occurring isothiocyanate, induces cell cycle arrest and apoptosis in HT29 human colon cancer cells. Cancer Res 60(5): 1426-1433.

126. Burn J, Chapman P, Bishop D, Mathers J (1998) Diet and cancer prevention: the concerted action polyp prevention (CAPP) studies. Proc Nutr Soc 57(2): 183-186.

127. Burn J, Gerdes A, Macrae F, Mecklin J, Moeslein G, et al. (2011) Long-term effect of aspirin on cancer risk in carriers of hereditary colorectal cancer: an analysis from the CAPP2 randomised controlled trial. Lancet 378(9809): 2081-2087.

128. Movahedi M, Bishop D, Macrae F, Mecklin J, Moeslein G, et al. (2015) Obesity, aspirin, and risk of colorectal cancer in carriers of hereditary colorectal cancer: a prospective investigation in the CAPP2 study. J Clin Oncol 33(31): 3591-3597.

129. Chung Y, Bae Y, Lee S (2003) Molecular ordering of ROS production, mitochondrial changes, and caspase activation during sodium salicylate-induced apoptosis. Free Radic Biol Med 34(4): 434-442.

130. Liao X, Lochhead P, Nishihara R, Morikawa T, Kuchiba A, et al. (2012) Mitochondrial changes, and caspase activation during sodium salicylate treatment activates survival signaling in nontumorigenic NCM460 colon cells but apoptotic signaling in tumorigenic HCT116 colon cells. Nutr Cancer 63(2): 248-255.

131. Cooper D, Webb D, JC P (1997) Evaluation of the potential for oles to affect the availability of dietary phytochemicals. J Nutr 127(8 Suppl): 1699S-1709S.

132. Cooper D, Webb D, JC P (1997) Evaluation of the potential for oles to affect the availability of dietary phytochemicals. J Nutr 127(8 Suppl): 1699S-1709S.

133. Lawrence J, Peter R, Baxter G, Robson J, Graham A, et al. (2003) Urinary excretion of salicylic and salicylic acids by non-vegetarians, vegetarians and patients taking low-dose aspirin. J Clin Pathol 56(9): 651-653.

134. Vucenik I, Shamsuddin A (2006) Protection against cancer by dietary IP6 and inositol. Nutr Cancer 55(2): 109-125.

135. Druzic J, Juricic J, Perko Z, Kraljevic D (2004) IP6 + Inositol as adjuvant to chemotherapy of colon cancer: our clinical experience. Anticancer Res 24(5): 3474-3475.

136. Kapral M, Wawrzynk J, Jurzak M, Dymitruk D, Weglara L (2010) Evaluation of the expression of metalloproteinases 2 and 9 and their tissue inhibitors in colon cancer cells treated with phytic acid. Acta Poloniae Pharmaceutica 67(6): 625-629.

137. Graf E, Eaton JW (1993) Suppression of colonic cancer by dietary phytic acid. Nutr Cancer 19(1): 11-19.

138. Nortsaal S, Norhaizan M, Hairuzah I, Norashareena M (2010) Anticarcinogenic efficacy of phytic acid extracted from rice bran on azoxymethane-induced colon carcinogenesis in rats. Exp Toxicol Pathol 62(3): 259-268.

139. Shafie N, Mohd Esa N, Ithnin H, Md Akim A, Saad N, et al. (2013) Preventive inositol hexaphosphate extracted from rice bran inhibits colorectal cancer through involvement of Wnt/β-catenin and CDX-2 pathways. Biomed Res Int 2013: 681027.

140. Burkitt DP (1971) Epidemiology of cancer of the colon and rectum. Cancer 28(1): 3-13.

141. Bingham SA (1990) Mechanisms and experimental and epidemiological evidence relating dietary fibre (non-starch polysaccharides) and starch to protection against large bowel cancer. Proc Nutr Soc 49(2): 153-171.

142. Young G, Hu Y, Leu R, Nyskohus L (2005) Dietary fibre and colorectal cancer: A model for environment-gene interactions. Mol Nutr Food Res 49(6): 571-584.

143. Slavin JL (2000) Mechanisms for the Impact of Whole Grain Foods on Cancer Risk. J Am Coll Nutr 19(3 Suppl): 300S-307S.

144. Rowland I (1999) Toxicological implications of the normal microflora. In: Tannock GW, ed. Med Imp Normal Microflora. Dordrecht, Kluwer Academic Publishers, USA.

145. Hollar M, Burnett-Hartman A, Lampe J (2014) Gut microbes, diet, and cancer. Cancer Treat Res 159: 377-399.

146. Bultman SJ (2017) Interplay between diet, gut microbiota, epigenetic events, and colorectal cancer. Mol Nutr Food Res 61(1).

147. Bingham S, Hughes R, Cross A (2002) Effect of white versus red meat on endogenous N-nitrosation in the human colon. Nutr Cancer 60(5): 153-171.

148. Vucenik I, Shamsuddin A (2006) Protection against cancer by dietary IP6 and inositol. Nutr Cancer 55(2): 109-125.

149. Bos JL (1989) ras oncogenes in human cancer: a review Cancer Res 49(17): 4682-4689.

150. Silvester K, Cummings J (1995) Does digestibility of meat protein help explain large bowel cancer risk? Nutr Cancer. 24(3): 279-288.

151. Hughes R, Cross A, Pollock J, Bingham S (2001) Dose-dependent effect of dietary meat on endogenous colonic N-nitrosation. Carcinogenesis 22(1): 199-202.

152. Hebels D, Sveje K, de Kok M, van Herwijnen MH, Kuhnle GG, et al. (2012) Red meat intake-induced increases in fecal water genotoxic activity and cancer risk. Carcinogenesis 33(11): 1781-1788.

153. Druzic J, Juricic J, Perko Z, Kraljevic D (2004) IP6 + Inositol as adjuvant to chemotherapy of colon cancer: our clinical experience. Anticancer Res 24(5): 3474-3475.

154. Healy B, Sveje K, de Kok M, van Herwijnen MH, Kuhnle GG, et al. (2012) Red meat intake-induced increases in fecal water genotoxic activity and cancer risk. Carcinogenesis 33(11): 1781-1788.

155. Blaser MJ (2008) Understanding microbe-induced cancers. Cancer Prev Res (Philadel) 1(1): 15-20.
154. Cross A, Pollock J, Bingham S (2003) Haem, not protein or inorganic iron, is responsible for endogenous intestinal N-nitrosation arising from red meat. Cancer Res 63(10): 2358-2360.

155. Hughes R, Pollock J, Bingham S (2002) Effect of vegetables, tea, and soy on endogenous N-nitrosation, fecal ammonia, and fecal water genotoxicity during a high red meat diet in humans. Nutr Cancer 42(1): 70-77.

156. Attene-Ramos M, Wagner E, Pleva M, Gaskins H (2006) Evidence that hydrogen sulfide is a genotoxic agent. Mol Cancer Res 4(1): 9-14.

157. Deplancke B, Gaskins H (2003) Hydrogen sulfide induces serum-independent cell cycle entry in non-transformed rat intestinal epithelial cells. PASEB J 17(10): 1310-1312.

158. Huycke M, Gaskins HR (2004) Commensal bacteria, redox stress, and colorectal cancer: mechanisms and models. Exp Biol Med (Maywood) 229(7): 586-597.

159. Christl S, Eisner H, Dusel G, Kasher H, Scheppach W (1996) Antagonistic effects of sulfide and butyrate on proliferation of colonic mucosa: a potential role for these agents in the pathogenesis of ulcerative colitis. Dig Dis Sci 41(12): 2477-2481.

160. Rodiger WE (1998) Decreased sulphur amino acid intake in ulcerative colitis. Lancet 351(9115): 1555.

161. Rodiger WE, Moore J, Babidge W (1997) Colonic sulfide in pathogenesis and treatment of ulcerative colitis. Dig Dis Sci 42(8): 1571-1579.

162. Attene-Ramos M, Wagner E, Gaskins H, Pleva M (2007) Hydrogen sulfide induces direct radical-associated DNA damage. Mol Cancer Res 5(5): 455-459.

163. O’Keefe S, Carrim Y, van der Merwe C, Hylemon P, Hertzler S (2004) Differences in Diet and Colonic Bacterial Metabolism That Might Account for the Low Risk of Colon Cancer in Native Americans Compared with Americans. J Nutr 134: 3521S–3547S.

164. Deplancke B, Finster K, Graham W, Collier CT, Thurmond JE, et al. (2003) Gastrointestinal and microbial responses to sulfate-supplemented drinking water in mice. Exp Biol Med (Maywood) 228(4): 424-433.

165. Magee E, Curno R, Edmond L, Cummings J (2004) Contribution of dietary protein and inorganic sulfur to urinary sulfate: toward a biomarker of inorganic sulfur intake. Am J Clin Nutr 80(1): 137-142.

166. Cani P, Neyrinck A, Fava F, Knauf C, Burcelin R, et al. (2007) Selective increases of bifidobacteria in gut microflora induce high-fat-diet-induced diabetes in mice through a mechanism associated with endotoxaemia. Diabetologia 50(11): 2374-2383.

167. Delzenne N, Cani P (2011) Interaction between obesity and the gut microbiota: relevance in nutrition. Ann Rev Nutr 31: 35-51.

168. de Wit N, Derrien M, Bosch-Veuremen H, Oosterink E, Keshkhar S, et al. (2012) Saturated fat stimulates obesity and hepatic steatosis and affects gut microbiota composition by an enhanced overflow of dietary fat to the distal intestine. Am J Physiol Gastrointest Liver Physiol 303(5): S589-S599.

169. Cani P, Amar J, Iglesias M, Poggi M, Knauf C, et al. (2007) Metabolic endotoxemia initiates obesity and insulin resistance. Diabetes 56(7): 1761-1772.

170. Creey S, McTernan P, Kusminski C, Fisher IM, Da Silva N, et al. (2007) Lipopolysaccharide activates an innate immune system response in human adipose tissue in obesity and type 2 diabetes. Am J Physiol Endocrinol Metab 292(3): E740-E747.

171. Cammarota R, Bertolini V, Pennesi G,ucci EO, Gottiard O, et al. (2010) The tumor microenvironment of colorectal cancer: stromal TLR-4 expression as a potential prognostic marker. J Transl Med 8: 112.

172. Fukata M, Abreu M (2007) TLR-4 signalling in the intestine in health and disease. Biochem Soc Trans 35(Pt 6): 1473-1478.

173. Abreu MT (2010) Toll-like receptor signalling in the intestinal epithelium: how bacterial recognition shapes intestinal function. Nat Rev Immunol 10(2): 131-144.

174. Manco M, Putignani L, Bottazza G (2010) Gut microbiota, lipopolysaccharides, and innate immunity in the pathogenesis of obesity and cardiovascular risk. Endocr Rev 31(6): 817-844.

175. Pastor Rojo O, López San Román A, Albéniz Arbizu E, de la Hera Martínez A, Ripoll Sevillano E, et al. (2007) Serum lipopolysaccharide-binding protein in endotoxemic patients with inflammatory bowel disease. Inflamm Bowel Dis 13(3): 269-277.

176. Chen R, Luo F, Wang Y, Tang J, Liu YS (2011) LBP and CD14 polymorphisms correlate with increased colorectal carcinoma risk in Han Chinese. World J Gastroenterol 17(18): 2326-2231.

177. Bernstein C, Holubec H, Bhattacharyya A, Nguyen H, Payne C, et al. (2011) Carcinogenicity of deoxycholate, a secondary bile acid. Arch Toxicol185(8): 863-871.

178. Mower H, Ray R, Shoff R, Stemmermann G, Nomura A, et al. (1979) Fecal bile acids in two Japanese populations with different colon cancer risks. Cancer Res 39(2 Pt 1): 328-331.

179. Bayerdörffer E, Mannes G, Richter W (1993) Increased serum deoxycholic acid levels in men with colorectal adenomas. Gastroenterol. 104(1): 145-151.

180. Bayerdörffer E, Mannes G, Ochsennkühn T, Dirscheld P, Paumgartner G (1994) Variation of serum bile acids in patients with colorectal adenomas during a one-year follow-up. Digestion 55(2): 121-129.

181. Reddy B, Weisburger J, Wynder E (1975) Effect of high-risk and low-risk diets for colon carcinogenesis on focal microflocs and steroids in man. J Nutr 105(7): 878-884.

182. Reddy BS (1981) Diet and excretion of bile acids. Cancer Res 41(9 Pt 2): 3766-3768.

183. Hague A, Elder D, Hicks D, Parakasova C (1995) Apoptosis in colorectal tumour cells: induction by the short chain fatty acids butyrate, propionate and acetate and by the bile salt deoxycholate. Int J Cancer 60(3): 400-406.

184. Reddy B, Hedges A, Laakso K, Wynder E (1978) Metabolic epidemiology of large bowel cancer: fecal bulk and constituents of high-risk North American and low-risk Finnish population. Cancer 42(6): 2832-2838.

185. Reddy B, Watanabe K, Sinaiifl A (1980) Effect of dietary wheat bran, alfalfa, pectin and carrageenan on plasma cholesterol and fecal bile acid and neutral sterol excretion in rats. J Nutr 110(6): 1247-1254.

186. O’Keefe SJ (2016) Diet, microorganisms and their metabolites, and colon cancer. Nat Rev Gastroenterol Hepatol 13(12): 691–706.

187. Macdonald R, Wagner K (2012) Influence of dietary phytochemicals and microbiota on colon cancer risk. J Agric Food Chem 60(27): 6728-6735.

188. Kristal A, Lampe J (2002) Brassica vegetables and prostate cancer risk: a review of the epidemiological evidence. Nutr Cancer 42(1): 1-9.

189. Braband A, Edwards C (1994) Isolation of glucosinolates from raw cruciferous vegetables: a potential role for these agents in the pathogenesis of colorectal cancer. Cancer Res. 39(2 Pt 1): 328-331.

190. Elfoul L, Rabot S, Khelifa N, Quinsac A, Duguay A, et al. (2001) Formation of allyl isothiocyanate from sinigrin in the digestive tract of rats. J Nutr 131(6): 1776-1782.
191. Hokst B, Williamson G (2004) A critical review of the bioavailability of glucosinolates and related compounds. Nat Prod Rep 21(3): 425-447.

192. Navarro S, Li F, Lampe JW (2011) Mechanisms of action of isothiocyanates in cancer chemoprevention: an update. Food Funct 2(10): 579-587.

193. Myzak M, Tong P, Dashwood W, Dashwood R, Ho E (2007) Sulforaphane inhibits HDAC activity in prostate cancer cells, retards growth of PC3 xenografts, and inhibits HDAC activity in human subjects. Exp Biol Med (Maywood, NJ) 232(2): 227-234.

194. Simpson H, Campbell B (2015) Review article: dietary fibre-microbiota interactions. Aliment Pharmacol Ther 42(2): 158-179.

195. Lin D, Peters B, Friedlander C, Freimann H, Goedert J, et al. (2018) Association of dietary fibre intake and gut microbiota in adults. Br J Nutr 120(9): 1014-1022.

196. Fry S (2004) Primary cell wall metabolism: tracking the careers of wall polymers in living plant cells. New Phytol 161(3): 641-675.

197. Chassard C, Lacroix C (2013) Carbohydrates and the human gut microbiota. Cur Opin Clin Nutr Metab Care 16(4): 453-460.

198. Lattimer J, Haub M (2010) Effects of dietary fiber and its components on metabolic health. Nutr 2(12): 1266-1289.

199. Macfarlane G, Gibson G (1997) Carbohydrate fermentation, energy transduction and gas metabolism in the human large intestine. In: Mackie R, White B, eds. Gastrointestinal Ecosystems and Fermentations. Chapman & Hall, New York, USA.

200. Flint H, Bayer E, Rincon M, Lamed R, White B (2008) Polysaccharide degradation by anaerobic bacteria: utilization by gut bacteria; potential for new insights from genomic analysis. Nat Rev Microbiol 6(2): 121-131.

201. Hamer H, Jonkers D, Venkata K, Vanhouvtin S, Troost F, et al. (2008) Review article: the role of butyrate on colonic function. Aliment Pharmacol Ther 27(2): 104-119.

202. Vinolo M, Rodrigues H, Nachbar R, Curi R (2011) Regulation of inflammation by short chain fatty acids. Nutrients. 3(10): 858-876.

203. Sengupta S, Muir J, Gibson P (2006) Does butyrate protect from colorectal cancer? J Gastroenterol Hepatol. 21(1 Pt 2): 228-236.

204. Donohoe D, Holley D, Collins L (2014) A gnotobiotic mouse model demonstrates that dietary fiber protects against colorectal tumorigenesis in a microbiota- and butyrate-dependent manner. Cancer Discov 4(12): 1387-1397.

205. Glick-Bauer M, Yeh MC (2014) The Health Advantage of a Vegan Diet: Exploring the Gut Microbiota Connection. Nutrients. 6(11): 4822-4838.

206. Zimmer J, Lange B, Frick J, Sauer H, Zimmermann K, et al. (2012) A vegan or vegetarian diet substantially alters the human colonic faecal microbiota. Eur J Clin Nutr 66(1): 53-60.

207. Banola V, Ghosh A, Kapardar R, Lal B, Cheema S, et al. (2017) Gut microbial diversity in health and disease: experience of healthy Indian subjects, and colon carcinoma and inflammatory bowel disease patients. Microb ecol health dis. 28(1): 1224-47.

208. Zhu Y, Wu H, Wang P, Savas S, Woodmow J, et al. (2013) Dietary patterns and colorectal cancer recurrence and survival: a cohort study. BMJ Open 3(e002270).

209. Lanza E, Hartman T, Albert P, Shields R, Slatery M, et al. (2006) High Dry Bean Intake and Reduced Risk of Advanced Colorectal Adenoma Recurrence among Participants in the Polyp Prevention Trial. J Nutr. 136(7): 1896-1903.

210. Song M, Wu K, Meyerhardt J, Ogino S, Wang M, et al. (2018) Fiber intake and survival after colorectal cancer diagnosis. JAMA Oncol 4(1): 71-79.

211. Jiang R, Manson J, Stampfer M, Liu S, Willett W, et al. (2002) Nut and peanut butter consumption and risk of type 2 diabetes in women. JAMA. 288(20): 2554-2560.

212. Salas-Salvadó J, Fernández-Ballart J, Ros E, Martínez-González M, Fito M, et al. (2008) Effect of a Mediterranean diet supplemented with nuts on metabolic syndrome status: one-year results of the PREDIMED randomized trial. Arch Inter Med 168(22): 2449-2458.

213. Casas-Agustench P, Bulló M, Ros E, Basora J, Salas-Salvadó J (2011) Cross-sectional association of nut intake with adiposity in a Mediterranean population. Nutr Metab Cardiovasc Dis 21(7): 518-525.

214. Kelly JJ, Sabaté J (2006) Nuts and coronary heart disease: an epidemiological perspective. Br J Nutr 96(Suppl 2): S61-S67.

215. Ibarrola-Jurado N, Bulló M, Guach-Ferré M, Ros E, Martínez-González M, et al. (2013) Cross-sectional assessment of nut consumption and obesity: metabolic syndrome and other cardiometabolic risk factors: the PREDIMED study. PLoS One 8(2): e57367.

216. González C, Salas-Salvadó J (2006) The potential of nuts in the prevention of cancer. Br J Nutr 96(Suppl 2): S97-S99.

217. Falasa M, Casari I, Maffucci T (2014) Cancer Chemoprevention with Nuts. J Natl Cancer Inst 106(9): dju238.

218. Falasa M, Casari I (2012) Cancer chemoprevention by nuts: evidence and promises. Front Biosci 4: 109-120.

219. Bao Y, Han J, Hu F, Giovannucci E, Stampfer M, et al. (2013) Association of nut consumption with total and cause-specific mortality. New Engl J Med 369(21): 2001-2011.

220. Guach-Ferré M, Bulló M, Martínez-González M, Ros E, Corella D, et al. (2013) Frequency of nut consumption and mortality risk in the PREDIMED nutrition intervention trial. BMC Med 11: 164.

221. Fadelu T, Niedzwiecki D, Zhang S, Ye X, Saltz L, et al. (2017) Nut consumption and survival in stage III colon cancer patients: Results from CALGB 89803 (Alliance). J Clin Oncol 36(11): 1112-1120.

222. Bao Y, Han J, Hu F, Giovannucci E, Willett W, et al. (2013) Nut consumption and risk of pancreatic cancer in women. Br J Cancer 109(11): 2911-2916.

223. Gupta S, Kim J, Prasad S, Aggarwal B (2010) Regulation of survival, proliferation, invasion, angiogenesis, and metastasis of tumor cells through modulation of inflammatory pathways by nutraceuticals. Cancer Metastasis Rev 29(3): 405-434.

224. Gicic B, Boeing H, Toth R, Böhm J, Habermann N, et al. (2018) Associations between dietary patterns and longitudinal quality of life changes in colorectal cancer patients: The ColoCare Study. Nutr Cancer 70(1): 51-60.

225. Rose S, Strombom A (2018) A comprehensive review of the prevention and treatment of heart disease with a plant-based diet. J Cardiol Cardiovasc Ther 12(5): 55567.

226. Strombom A, Rose S (2017) The prevention and treatment of Type II Diabetes Mellitus with a plant-based diet. Endocrin Metab Int J 5(5): 001 38.

227. Barnard N, Cohen J, Jenkins D, Turner-McGrievy G, Gloede L, et al. (2006) A low-fat vegan diet improves glycemic control and cardiovascular risk factors in a randomized clinical trial in individuals with type 2 diabetes. Diabetes Care 29(8): 1777-1783.

228. Lancet (1998) Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes.
(UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. Lancet 352(9131): 854-865.

229. Jenkins D, Kendall C, Marchie A, Faulkner D, Wong J, et al. (2005) Direct comparison of a dietary portfolio of cholesterol-lowering foods with a statin in hypercholesterolemic participants. Am J Clin Nutr 81(2): 380-387.