

Colon Cancer Prevention with a Plant-Based Diet

I. Executive Summary

It has long been known that vegetarians have a substantially reduced risk of colon cancer. Several studies have shown that vegetarians have a reduced risk of colon cancer of 46%-88%, and, as might be expected, a 54% reduced risk of colon adenoma, plus a 200% reduced risk of advanced adenoma. Vegetarians also have a lower prevalence of risk factors for colon cancer. These include a much lower risk of hyperinsulinemia secondary to metabolic syndrome, lower risk of obesity, and a much lower risk of Crohn's disease. Vegetarians also have lower levels of CRP (cardio reactive protein) indicating a lower inflammatory status. This has also been correlated with a better prognosis for colon cancer.

Processed meat and red meat have recently been shown to be carcinogenic for colon cancer. Acting on this evidence, the World Health Organization and the ACIR, based on the strength of evidence, have declared processed meat a Class I Carcinogen and red meat as a probable carcinogen.

The pathogenic mechanisms showing how processed meat and red meat cause colon cancer, and the chemoprotective mechanisms whereby plant foods help protect against cancer, have now been elucidated. Specific exogenous colon carcinogens contained in meat have been identified, including heterocyclic amines (HCAs), polyaromatic hydrocarbons (PAHs), nitrites, and polychlorinated biphenyls (PCBs). The chemoprotective mechanisms of plant foods are through the actions of phytochemicals such as sulforaphane, salicylates and phytic acid. Furthermore, the evidence for the role of dietary fiber in helping to reduce the risk of colon cancer has now been classified as "Convincing" by the World Health Organization.

Hyperinsulinemia and raised levels of IGF-1 (insulin like growth factor) have both been shown to promote the growth of colon cancer tumors. High CRP levels are associated with an increased risk of both adenoma and advanced adenoma. Several matrix metallo proteinases (MMPs) have also been shown to play a role in the pathogenesis of colon cancer. Vegetarians have lower levels of insulin, IGF-1, CRP and MMPs, thus reducing the risk of colon cancer even further.

The role played by the colon's bacterial flora in the etiology of colon cancer has recently been elucidated. It has been shown that a meat-centered diet produces a bacterial profile that is inflammatory, and endogenously produces carcinogens such as Nitroso amines, hydrogen sulfide, and secondary bile acids. However, the flora of those on a plant-based diet produce anti-inflammatory byproducts such as butyrate.

Thus, we see that vegetarians have lower levels of colon cancer carcinogens, and pathogenic factors involved in the carcinogenic process than meat eaters, and higher levels of protective

factors as a result of consuming a greater quantity of plant foods. This helps explain the lower risk of colon cancer that vegetarians have been shown to have in epidemiological studies.

While the effect of a vegetarian diet on recurrence has not been studied, studies of the risk for recurrence of colon cancer have shown an 85% increased risk by consuming processed meat, and the regular consumption of certain plant-foods such as legumes and tree nuts have been shown to greatly reduce the risk of recurrence.

While colonoscopy is valuable as a diagnostic method, and polypectomy is valuable for secondary prevention, a vegetarian diet can provide primary prevention of colon cancer. Given the incidence of colon cancer, and given that it is the second most common cause of cancer mortality, primary prevention would seem particularly desirable. Making primary and secondary prevention of colon cancer with a vegetarian diet all the more desirable is that it is also a safe and efficacious prophylaxis and treatment for common comorbidities such as coronary artery disease and type II diabetes.

II. Introduction

This article reviews the primary and secondary prevention of colon cancer with a vegetarian diet. We first examine the epidemiologic evidence for the reduced risk of colon cancer that vegetarians have. We cover the pathogenic mechanisms by which processed and red meat cause colon cancer, and several of the ways plant foods and their phytonutrients are chemo-protective against colon cancer. Several carcinogens are addressed, along with some phytonutrients that have a protective role. The effect of processed meat on raising the risk of colon cancer recurrence is also addressed. Finally, we discuss the role of a vegetarian diet as it relates to colonoscopy, and its ability to prevent and treat common comorbidities. Please note, this article does not cover less common pathologies such as Familial Adenomatous Polyposis, Turcot Syndrome and Lynch Syndrome.

III. Prevention of Colorectal Cancer

A. 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, 3, 4, 5, 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, 9)

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, 10, 11, 12) 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. (13)

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 100g 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. (14)

It has been well documented that most colorectal cancers arise from colorectal adenoma by a process referred to as the adenoma–carcinoma sequence. (15) 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. (16) 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. (17)

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. (18) According to the author, the meat-eaters in this study were consuming less than 2oz 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. (18)

B. 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.

1. Dietary risk factors

Processed meat was classified by the World Health Organization International Agency for Research on Cancer as carcinogenic to humans (Group 1), based on strength of evidence in humans that the consumption of processed meat causes colorectal cancer. (19) Red meat was classified as probably carcinogenic to humans (Group 2A). (19)

2. 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. (20) 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 hyperinsulinemic exposure in colon carcinogenesis. (2, 17)

Vegetarians have a 70-80% reduced risk of hyperinsulinemia (21) and lower insulin levels. (22, 23) This likely is one of the factors causing their reduced risk of colon cancer.

3. Obesity

High body mass index (BMI) is a risk factor for colon cancer. (24)

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. (25) 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. (26) A study of German vegans found an average BMI of 22.3. (27) 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. (28) One study found the risk of being overweight or obese is 65% less for vegans and 46% less for vegetarians. (29)

4. Crohn's Disease

There is an elevated risk of colon cancer in patients with Crohn's Disease. (30) However, a vegetarian diet reduces risk of Crohn's disease by 70% in girls, and 80% in boys. (31)

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.

C. 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. (32) They have various cancer impeding activities, such as reducing DNA damage via antioxidant properties or interacting with inflammation pathways. (33) In this article we focus on just two phytochemicals as examples, sulforaphane and salicylate. However, there are many others that have chemo-protective effects.

1. 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.

2. Salicylates

The role of aspirin in cancer has been extensively investigated. (34, 35) 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. (36, 37, 38, 39, 40) 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. (39) 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 (COX-2). (37)

After absorption, aspirin is very rapidly hydrolyzed to salicylic acid (2-hydroxybenzoic acid). (41) 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. (42, 43)

3. Fiber

Inverse associations between dietary fiber intake and colorectal cancer risk have been reported in ecological and case-control studies. (44, 45) Inverse associations for fiber and colorectal adenoma (46) and colorectal cancer (47, 48, 49, 50) have also been reported in well-designed prospective studies. In the EPIC study, after an average 6.2 years of follow-up 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. (51, 52)

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”. (53)

Vegetarians and vegans, consuming a wide variety of plant-based foods, will naturally consume much more fiber than meat-eaters.

IV. 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.

Pathogenic factors explained below, include:

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.

A. Pathogenic Mechanisms

1. 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, (54, 55) heterocyclic amines (HCAs), (54, 56) polycyclic aromatic hydrocarbons (PAHs), (57) nitrites and nitrates, (54, 58) and organochlorine compounds such as PCBs. (59) HCAs, PAHs, nitrites and nitrates may all be involved in colorectal cancer etiology. (60)

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 (IV.C.2.a).

Heterocyclic amines are mutagenic compounds formed when muscle meat is cooked using high-temperature methods, such as grilling, barbequing, and pan-frying. (61) 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. (62)

HCAs, measured using urine or leukocyte assays, have been associated with colon adenoma. (63, 64, 65) 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. (66, 67, 68, 69, 70, 71, 72, 73, 74, 75) In one study, women with genotypes associated with rapid acetylation of meat-associated carcinogens, had a particularly high risk of colorectal cancer associated with red meat intake. (76) 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. (77, 78)

Meat that is cooked above an open flame, as with grilling and barbecuing, results in fat and juices dripping onto the fire, yielding flames that contain PAHs. These PAHs then adhere to the surface of the meat. (62) 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. (79) Studies of PAH exposure indicate that the target organs for PAH compounds are the lung, oropharynx, breast and genitourinary and gastrointestinal tracts. (80) 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. (81, 82)

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. (60)

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. (83)

Sodium nitrites 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 nitrites—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. (84, 58) See section IV.C.2.a 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. (85, 86, 87) 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. (59)

2. 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. (88)

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. (89) 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. (88)

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). (90, 91) 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. (91, 92)

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. (93, 94) 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. (95)

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. (96) 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. (97)

3. Insulin-Like Growth Factor

The insulin-like growth factor (IGF) system is a multifactorial signaling network that modulates energy metabolism, cell growth, and cancer. (93) 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). (98)

Breast, ovarian, prostate, lung, and colon cancer are the tumor tissues where the IGF system has been directly linked to tumor development and progression. (99, 100) 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. (99, 100, 101)

Hyperinsulinemia has an effect on cell proliferation, not only through insulin receptor signaling, but also through the amplification of IGF-1 effect. (101, 102) 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. (103) Similar results have been obtained studying vegan men. (104)

4. 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, 2.24 for stage IV. (105)

A study of CRP and adenoma showed a positive association between plasma CRP concentration and the prevalence of colorectal adenoma. (106) 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. (107)

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. (108)

The ability of a plant-based diet to lower CRP levels, and the fact that vegetarians have lower CRP levels (109), 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. (110) The fact that vegetarians have lower levels of CRP, decreases their chance of a poor prognosis for colon cancer.

5. Matrix Metalloproteinases

Matrix metalloproteinases (MMPs) consist of a multigene family of zinc dependent extracellular matrix (ECM) remodeling endopeptidases 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. (111)

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. (112, 113)

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. (112, 113)

B. 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.

1. 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. (114)

Because of its lipophilicity (115) and molecular size, SFN is likely to passively diffuse into the enterocytes. (116) 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. (117) 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. (118)

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. (119)

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. (120) 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. (121)

2. Salicylates

The cancer preventive action of aspirin is due to its principal metabolite, salicylic acid. Sodium salicylate induces apoptosis in cancer cells. (122) 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. (123) 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). (123) Two aspirins taken daily for two years reduced CRC by more than 50% five years later. Obese participants were particularly protected. (124)

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. (125) 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. (126) 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- κ B), (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 prevent cancer. (127)

Dietary salicylates can have the same effect. (128, 43) 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. (129) Lawrence et. al. show that urinary excretion of salicyluric acid (SU) and salicylic acid (SA) is significantly increased in vegetarians compared with non-vegetarians. (130) They previously reported that serum salicylic acid was also significantly increased in vegetarians compared with non-vegetarians. (129) 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.

3. 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. (131)

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 inositols were added along with conventional chemotherapy, colon cancer patients experienced significantly less side effects than controls, as reported in a pilot study. (132)

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. (133) Vegetarians have lower levels of MMP-2 (112) 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. (134)

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. (135)

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. (136)

These are elements of rapidly accumulating data from animal models, indicating that dietary supplementation with phytic acid may provide substantial protection against experimentally induced colonic 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 colonic carcinogenesis. (134)

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. (131)

Since phytic acid can only be obtained from plant foods, vegetarians and especially vegans, naturally consume higher levels of phytic acid than meat eaters.

4. Fiber

The possible protective association between dietary fiber intake and colorectal cancer was first proposed by Burkitt in 1971. (137) 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. (138, 139, 140)

The role of fiber is further discussed in the Microbiome section below.

C. The Role of the Gut Microbiome

1. 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. (141)

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). (142)

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:

- i. harvesting otherwise inaccessible nutrients and/or sources of energy from the diet (i.e., fermentation of dietary fibers and resistant starch),
- ii. metabolism of xenobiotics, both potentially beneficial or detrimental (i.e., dietary constituents, drugs, carcinogens, etc.),
- iii. renewal of gut epithelial cells and maintenance of mucosal integrity, and
- iv. 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. (143)

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. (142)

2. 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.

a) 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. (55) These include protein and other nitrogenous residues which allow for increased gut bacterial production of N-nitroso compounds (NOC). (144) 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. (145) NOC can form DNA adducts which induce mutations. For example, it has been shown that some NOC are alkylating 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. (145)

Diet can influence NOC concentrations. Meat consumption increases the amount of nitrogenous residues in the colon, (146) and in a controlled feeding study in eight men, there was a dose–response between intake of meat and fecal concentrations of NOC. (147) 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. (148) 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. (149, 150) 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. (150) The addition of soy to the diet statistically significantly suppressed fecal NOC. (151)

b) Hydrogen sulfide (H₂S)

Hydrogen sulfide (H₂S) is produced by sulfate-reducing bacteria (SRB) and has been shown to have both cytotoxic and genotoxic effects in cell culture studies. (152, 153, 154) For example, using a modified comet assay, Attene-Ramos et al. (152) showed that H₂S resulted in genomic DNA damage. H₂S has also been shown to prevent the oxidation of butyrate by colonic epithelial cells, thereby reducing ATP formation and energy harvest. (155) This lowers the absorption of ions, mucus formation, and cellular detoxification. Roediger et al. (156, 157) reported decreased fatty acid oxidation in colonocytes exposed to H₂S, and there is evidence that sulfide alters cellular redox potential which, in turn, alters cell proliferation. (153)

The role of SRB in inflammatory bowel disease and colorectal cancer has been evaluated in several epidemiologic and clinical studies. (142) Genomic instability associated with sporadic colon cancer and ulcerative colitis, a risk factor for colon cancer, is thought to result in part from H₂S exposure. (158) In a population-based study, the prevalence of SRB was associated with the diets of groups having higher rates of colon cancer. (159)

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 (SO₄ in water) contribute to H₂S production. (160) In a controlled feeding study, Magee et al. (161) showed that H₂S was significantly related to the amount of meat protein consumed.

c) Dietary fat

Cani et al. (162) 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 coccoides 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. (162, 163) In addition, de Wit et al. (164) 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 (162, 165, 166) and colorectal cancer. (167) LPS acts through toll-like receptor-4 (TLR-4), a PRR associated with innate immunity, which triggers TGF- β -mediated pathways. (168, 169) This leads to the expression of various genes that promote neoplasia, including those of growth factors and inflammatory mediators. Serum LPS binding protein (LBP), a protein that binds LPS upon activation of TLR-4, is correlated with circulating concentrations of LPS, (170, 171) and a recent prospective study showed that polymorphisms in the LBP gene were associated with increased colorectal cancer risk. (172)

d) Deoxycholic acid (DCA)

The secondary bile acid, deoxycholic acid (DCA), a colonic bacterial transformation product, has been implicated in gallstone formation and colorectal carcinogenesis. (173, 174)

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. (175, 176) Vegetarian diets result in significantly lower levels of DCA than the standard American diet. (177, 178) 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, (179) 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. (180, 181)

3. 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.

a) 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. (182)

b) Polyphenols

Plant-derived polyphenols are active mediators of cellular events, targeting key carcinogenic pathways, and modulating colonic microbial populations. In turn, the colonic microorganisms 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. (183)

Consumption of cruciferous or Brassica vegetables has been shown to be inversely associated with risk of some cancers. (184) 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. (185, 186, 187)

Isothiocyanates (ITCs) have been shown to have anti carcinogenic properties both in vitro and in vivo. (188) 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 IV.B.2 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. (189)

c) 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. (190)

Dietary fiber of edible plants comprises insoluble and soluble carbohydrates including cellulose, lignin, and nonstarch polysaccharides such as hemicelluloses, pectins and arabinoxylan oligosaccharides. (191, 190) Other dietary fiber components include nondigestible oligosaccharides such as inulin and oligofructose, as well as resistant starch. (191, 190, 192) 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. (193) 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. (194, 195, 196) In particular, butyrate has been reported to be protective against development of colitis (197) and colorectal cancer. (198, 199)

4. 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. (200)

The vegan gut profile appears to be unique in several characteristics, including a reduced abundance of pathobionts 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. (200)

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. (200)

A recent, large-scale study by Zimmer et al. (201) 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. (177)

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. (202) This difference may help account for the lower risk vegetarians have of colon cancer.

V. 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%. (203)

However, certain plant foods, in particular beans 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%. (204)

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. (205, 206, 207, 208, 209) In addition, studies have suggested that nut consumption could also have a chemopreventive effect, especially on colorectal and prostate cancer. (210, 211) Recent epidemiological studies have confirmed an inverse association between frequent nut consumption and cancer mortality. (212, 213, 214)

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. (215)

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 (216, 217) and therefore can account for the anticancer properties of nuts.

VI. 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 polyps, 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. (218) 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. (219) 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.

It also 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. (220, 221)

When treating patients with a plant-based diet, physicians should also monitor those patients with such comorbidities, since a plant-based diet may well have a beneficial impact on these diseases as well. Physicians should 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 (222, 223) and is as efficacious for the treatment of hypercholesterolemia as the reductase inhibitor, Lovostatin. (224) Therefore, medications should be titrated as the treatment effects for comorbidities become evident.

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