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Review

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The role of plant-based nutrition in cancer prevention

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Abstract

Plant-based nutrition has been shown to protect against the 15 leading causes of death in the world, including many cancers, and may offer benefits as a disease modifying tool to improve the management and treatment of these conditions. Results on the effects of plant-based nutrition on breast, prostate, colorectal and gastrointestinal cancers have been the most extensively studied, and thus have the most published supporting evidence thus far. Whole foods plant-based diets have shown to significantly protect against these cancers, as well as additional cancers and other chronic disease states. Nutritional interventions in the prevention of various cancers offer a significant benefit to currently used medical therapies, and should be employed more often as an adjunct to first-line medical therapy. Although the effects of diet are becoming more well-known and the role of diet and lifestyle factors in health and disease is gaining more attention and emphasis, the benefits or detriments are still underestimated and undervalued.

Keywords: Vegan nutrition, plant-based diet, cancer, nutritional therapy

INTRODUCTION

In the United States and many other industrialized countries, the main causes of death are preventable[1]. In particular, our diet remains the number-one cause of premature death and the number-one cause of disability[2]. Populations consuming diets of mostly plant-based foods have been characterized by a marked reduction in mortality and age-adjusted incidence of many cancers common in Western society. These cancers include breast, prostate, colon, pancreas, ovary, and uterine endometrium cancers[3,4]. However, this phenomenon is becoming less prominent as the Westernized diet and lifestyle spread throughout the world. Reports by the International Agency for Research on Cancer, the cancer agency of the World Health Orga-

nization implicate red and processed meats as important carcinogens[5]. In contrast, other nutritional aspects such as high intake of fiber, fruits and vegetables have a protective effect on cancer[6-9]. While the importance of plant-based foods such as fruits, vegetables, nuts, seeds, and legumes as sources of nutrients is generally accepted, utilization of diet for prevention and management of disease is still uncommon. This is despite the fact that multiple observational and experimental research studies have demonstrated a significant protective effect of plant-based diets against the incidence of cancer as well as many other disease conditions including the 15 leading causes of death in the western world[10]. A recent comprehensive meta-analysis reported a significant protective effect of a vegetarian diet *vs.* the incidence from total cancer (-8%) while a vegan diet conferred a significant reduced risk (-15%) of incidence from total cancer[11].

Current treatment options for cancer include surgery, radiotherapy, and chemotherapy[12]. These cancer treatments impose a large financial burden not only on health care systems but also to patients themselves. Therefore, nutritional interventions should be used for prevention and could serve as a cost-effective and safe adjunct therapy to standard medical treatments. This review explores the existing evidence of the influence of diet on cancer incidence and progression with a specific focus on the effects of a reduction or total elimination of animal protein, in addition to notable bioactive compounds in plant foods that offer protection against cancers. Though plant-based nutrition has been shown to help prevent and improve survival in many cancers, our review will focus mainly on breast, prostate, colorectal and gastrointestinal (GI) cancers, since these are the classes that have the most supporting evidence for plant-based diets to date. We will also briefly touch on "other" cancers before our concluding section.

A PubMed search was conducted using terms such as vegan diet and cancer, vegetarian diet and cancer, plant-based nutrition and cancer, vegan diet and breast cancer, vegan diet and prostate cancer, vegan diet and GI cancer. Secondary search strategy included cross referencing articles as well as identifying potential resources from the Physicians Committee for Responsible Medicine nutrition guide for clinicians. Sources included systematic reviews and meta-analyses, as well as original studies with various methodologies such as longitudinal prospective cohort studies, randomized controlled trials, and case series.

PLANT-BASED NUTRITION AND BREAST CANCER

Next to skin cancer, the most common cancer among American women is breast cancer. Each year an estimated 250,000 are diagnosed (in addition to 2,500 cases in men), and 40,000 women as well as 460 men die from it[13]. Typically, imaging and early detection is emphasized in order to improve survival. However, early detection and screening does not prevent breast cancer, it simply picks up disease that already exists. Furthermore, modern imaging isn't good enough to detect cancer's earliest stages, thus what has come to be described by the medical community as "early detection", is unfortunately actually "late detection"[14]. For example, a breast cancer tumor must be the size of about 2 billion cells (30 doublings) in order to get picked up by a mammogram[15,16]. The main factor that determines doubling time, and thus the timing of when someone gets diagnosed with cancer, can range from 25 days[17] to over a thousand days[18]. This means that someone could be diagnosed anywhere between 2 and 100 years, and a primary determination as to where an individual falls on that timeline, may depend on what they eat.

Based on autopsy studies, as many as 39% of women in their 40's already have developed breast cancers that may simply be too small to detect by mammograms[19,20]. Breast cancers may even begin developing in utero due to a mother's diet[21]. Thus, waiting until diagnosis to start eating and living healthier, might be too late. Typically, someone is considered to be "healthy" if they haven't shown to have any pathologies or abnormalities on scans/diagnostic screening tests, and if they don't show any clinical symptoms of a disease state. However, if someone has been harbouring a malignancy for decades that was simply too small to be detected or to lead to significant noticeable clinical signs, can that individual truly be considered "healthy"? Since there is much more going on at a cellular level within the human body than scans may ever be able to

fully demonstrate, a more beneficial framework may be to look at living in a constant state of prevention and treatment, rather than waiting until a disease has progressed to the point of showing outward signs. Therefore, perhaps we should be living as if we already have the beginnings of disease in our bodies, because a diet and lifestyle of prevention may also be one of treatment for the potential occult diseases that we cannot yet see.

In 2014, the American Institute for Cancer Research (AICR) came up with 10 recommendations for cancer prevention[22]. The conclusion around diet was that the intake of primarily whole plant foods (vegetables, fruits, whole grains, beans) decreases the risk of many cancers and other disease states. Looking at breast cancer specifically, a 2013 study[23] that followed approximately 30,000 post-menopausal women with no history of breast cancer for 7 years showed that by achieving just 3 of 10 AICR recommendations (maintaining a normal body weight, limiting alcohol, and eating mostly plant-based), a 62% decreased risk of breast cancer was achieved. Additionally, the rate at which eating plant-based can change an individual's physiology is quite remarkable. In 2006, the effects of a healthy diet (plant-based) and lifestyle (walking every day) on tumor cell growth and apoptosis *in vitro* were tested[24]. Researchers found that within only 2 weeks of healthy living, participants blood samples were able to suppress cancer growth and kill 20%-30% more malignant cells than blood samples taken prior to the diet/lifestyle change. It was concluded that the cancer suppression effect could be attributed to decreased levels of insulin-like growth factor 1 (IGF-1) due to reduced intake of animal protein[25,26]. IGF-1 is a hormone crucial for cell growth, and the more IGF-1 presents in the blood stream, the higher ones risk for cancer development[27]. Therefore, it is hypothesized that by reducing animal intake, we reduce IGF-1 and boost our body's natural cancer defences[28]. In 2002, Ngo and colleagues found that after 11 days of reducing animal protein consumption, levels of circulating IGF-1 dropped by 20%, whereas levels of the cancer protective IGF-1 binding protein increased by 50%[25]. In terms of how much the intake of animal proteins must be reduced in order to obtain these protective effects, it is only those following a fully plant-based (vegan) diet that experience cancer protection due to decreased growth hormone and increased binding protein levels. Vegetarians who consume eggs and dairy do not have the same protective effect, because all animal proteins stimulate the production of IGF-1, regardless of if the source is from the muscle, eggs, or dairy[26,29].

Heterocyclic amines and breast cancer

Another substance besides IGF-1 that is found in animal products and contributes to cancer risk is heterocyclic amines (HCAs). Since an original paper in 1939, it has been found that cancer producing substances are present in animal products cooked in various forms at high temperatures (roasting, pan-frying, grilling, baking)[30]. HCAs are described by the National Cancer Institute as "chemicals found when muscle in meat, including beef, pork, fish, and poultry, is cooked using high-temperature methods"[31]. HCAs are formed when these high temperatures promote chemical reactions between components of muscle tissue, compounds that are lacking in plants and thus cooked veggie burgers/products do not contain measurable amounts of HCAs[32]. The longer the meat is cooked, the more HCAs produced, and results show that well-done meat is associated with increased risk of breast, colon, esophagus, pancreas, prostate and stomach[33]. This however, does not mean that less cooking time doesn't produce HCAs, and even baking chicken for 15 min at 350 degrees leads to the production of measurable amounts that lead to DNA damage and thus an increased risk for cancer development[34,35].

A number of studies, including the Long Island Breast Cancer Study Project and the Iowa Women's Health Study have demonstrated significant correlation between women eating more cooked meats and higher odds of developing breast cancer[36,37]. The Long Island study saw a 47% increased odds in women who ate more grilled, barbecue, or smoked meat across their lifetime, and the Iowa study saw a 5-fold increased odds of cancer occurrence in women who ate their meat "well-done". Studies have also shown a link between the amount of DNA damage in the breast tissue and fried meat consumption[38]. One mechanism behind this increased odds of breast cancer is that 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP), the most

abundant HCA in cooked meat, has potent estrogen-like effects and can contribute to cell growth almost as much as endogenous estrogen which is the hormone responsible for feeding most human breast cancer tumours[39]. After initial *in vitro* studies, in order to determine if HCAs actually make their way into women's breast ducts from their food, researchers measured levels of PhIP in subject's breast milk, and amounts were detected in concentrations known to be carcinogenic[40]. In another study, PhIP was found in hair samples of both meat-eating and vegetarian women, since HCAs are also found in other forms of animal proteins than just muscle tissue, such as fried eggs[41]. Therefore, in order to be protected from PhIP and other HCAs, eating a fully plant-based diet appears safest.

Preventing breast cancer with eating plants

Unfortunately, even post breast cancer diagnosis, most don't adopt the necessary dietary and lifestyle changes to combat their disease and prolong life, notably consuming more whole plant foods[42]. This is for various reasons ranging from lack of personal realization, failure of physicians to educate their patients or be educated enough themselves in the field of nutrition to accurately and adequately counsel patients on nutritional interventions for disease states. Making a couple simple changes, such as consuming just 5 or more servings of fruits and vegetables per day along with walking 30 min 6 days a week is shown to lead to a notable survival advantage, with 50% less risk of 2-year post-diagnosis mortality rates[43].

Some of the notable plant foods/components of plant foods that are particularly beneficial include fiber, greens, and flaxseeds. Studies have shown that women consuming 6 g or more of soluble fiber a day (equivalent of a cup of black beans) had a 62% risk reduction of breast cancer compared to those consuming less than 4 g. Notably, the effects seem to be more significant for the harder to treat estrogen receptor negative (ER-) tumors, where premenopausal women with high fiber intake had an 85% risk reduction[44]. Dozens of reports including case control and prospective cohort studies have reported similar findings, with the consensus being that the more plant-based one's diet, the better for one's health[45,46]. Results have associated every 20 g of fiber consumed per day with approximately a 15% risk reduction of breast cancer, however some suggest that the effects may only be achieved once a baseline of 20 g per day is achieved[47]. One might think that 20 g may not seem like very much, given that just one cup of split peas has 16 g, yet the average American women generally gets less than 15 g per day, with vegetarians slightly higher at 20 g, healthy vegetarians at 37 g, vegans at 46 g, and whole-food plant-based diets recommended as therapeutic interventions for many chronic disease averaging about 60 g[48-50]. These results paint a clear picture that individuals in America and Westernized countries around the world are fiber deficient, and an increase in fiber intake from whole foods (not supplements) can be of great benefit in improving health.

In the above mentioned Long Island women's study where cooked meat consumption was linked to a 47% increased risk of breast cancer, those who also had low intake of fruits and vegetables, had a 74% increased risk[36]. Higher fruit and vegetable intake is not only associated with better health and lifestyle habits overall, but there are many bioactive compounds in fruits and vegetables that protect against cancer. For example, cruciferous vegetables like broccoli boost the activity of detoxifying enzymes in the liver[51]. Research has shown that consumption of broccoli and brussels sprouts causes increased caffeine clearance, and it was discovered that the same happens with carcinogens. When feeding non-smokers pan-fried meat for 2 weeks in addition to 3 cups of broccoli and brussels sprouts, and measuring levels of HCAs in urine samples, liver clearance was increased[52]. Although consuming the same amount of carcinogens, significantly less came out in subject's urine, a finding consistent with the theory of cruciferous vegetables detoxifying ability. It was also found that liver function remained enhanced for up to 2 weeks after vegetable consumption ceased. However, choosing the veggie burger with no HCAs to detoxify in the first place is the safest option[53].

Next, flaxseeds, one of the first things considered to be health food, known for their rich source of omega-3 fatty acids, are also significant as a health product because of their lignan content, which is about 100 times more than other plant foods[54-56]. Lignans are a class of phytoestrogens that like other phytoestrogens,

modulate and suppress effects of endogenous estrogen, which is why they are used as a first line therapy for menstrual breast pain[57].

Regarding breast cancer risk, consumption of approximately one tablespoon of ground flaxseed daily can extend a women's menstrual cycle by about a day, meaning less lifetime estrogen exposure and less risk of breast cancer[57]. In terms of the biological action of flaxseeds, they actually contain lignan precursors, which then get activated by intestinal bacteria, a finding that may explain in part why women with frequent urinary tract infections and thus increased antibiotic consumption (killing natural as well as pathological gut flora) have higher risk of breast cancer[58].

In vitro as well as interventional studies have shown lignans to directly suppress the growth and proliferation of breast cancer cells[59]. In a 2010 National Cancer Institute funded study of 45 women with high breast cancer risk (due to either suspicious biopsies or previous breast cancer diagnoses) given 2 tablespoons of ground flaxseed per day, their cancer risk was found to be greatly reduced[60]. Compared to pre-study, needle biopsies post yearlong study showed fewer precancerous changes than before, and 80% had decreased levels of Ki-67, a biomarker for increased cell proliferation, suggesting that breast cancer risk can be significantly reduced by just adding a few tablespoons of ground flaxseeds to one's food each day. In considering women already diagnosed with breast cancer, women with higher serum lignan levels[61,62] and who consume more dietary lignans[63] show increased survival rates. Researchers hypothesize that this finding may be a result of the concurrent rise of the protein endostatin, which plays a role in starving tumors of their blood supply in the breasts of women who consume more lignans[64].

Because of positive preliminary studies with flaxseeds, randomized, double blind, placebo controlled trials were developed to test this treatment for breast cancer patients. Flaxseeds are one of the few food items that have ever been rigorously tested in clinical trials. The study population consisted of women scheduled for breast cancer surgery, divided into the experimental group, consuming one flaxseed containing muffin each day, and a control group consuming a placebo muffin without flaxseeds that looked and tasted the same[65]. Based on tumor biopsies taken about 5 weeks before, and then after surgery, women in the flaxseed group showed decreased tumor proliferation, increased cancer cell death rate, and lower c-erB2 scores which is a marker of cancer aggressiveness. Therefore, flaxseeds appeared to make tumors less aggressive and researchers concluded that "dietary flaxseed has the potential to reduce tumor growth in patients with breast cancer". Despite the promising results there has been a lack of translation of these findings and other studies showing similar results into clinical practice.

Soy and breast cancer

One way researchers discovered the effects of soy on breast cancer risk, is through population studies. It has been found that women in Asia are about 5 times less likely to develop breast cancer than North Americans[66]. Possible explanations may include green tea consumption which is known to decrease risk by about 30%[67], as well as increased mushroom consumption[68]. White mushrooms have been shown to block estrogen synthase enzymes *in vitro*, and researchers found that when comparing 1000 breast cancer patients to the same number of healthy controls, those who ate more than just one half of a mushroom per day experienced a 64% risk reduction over women who ate no mushrooms. Therefore, in combination with drinking half of a tea bag of green tea per day, eating mushrooms leads to a 90% risk reduction[69]. Furthermore, another factor accounting for the population discrepancies in breast cancer risk is increased soy consumption throughout the lifespan beginning in childhood in Asian individuals. Lifelong soy consumption offers the most protective effect, reducing breast cancer risk by 50%, compared to only a 25% risk reduction if soy is consumed beginning in adulthood[70].

The specific compound in soy that is significant in creating its breast cancer protection are isoflavones, a class of phytoestrogens. There is a common misconception that since estrogen is in word phytoestrogen,

these compounds have estrogen-like effects, which is not entirely true. Though phytoestrogens bind to the same receptors as endogenous estrogen, they have a weaker effect and thus actually act to block the effects of more powerful endogenous and animal product derived estrogen[71]. Of the human body's two kinds of estrogen receptors (ERs), endogenous estrogen has stronger affinity for alpha receptors, and phytoestrogens (plant estrogens) for beta receptors[72]. Because of the distribution of alpha and beta receptors in various tissues, estrogens (and phytoestrogens) have different effects depending on receptor distribution in tissues[73]. For example, estrogen has positive effects on the bones, but contributes to increased risk of breast cancer. For this reason, ideally the body would benefit from a selective ER modulator, allowing positive estrogenic effects in some tissues (bones), and anti-estrogen effects in others (breast). Phytoestrogens appear to act in that way[73], and soy for example, lowers breast cancer risk (an anti-estrogenic effect) yet reduces menopausal symptoms such as hot flashes (a pro-estrogenic effect)[74,75].

In addition to preventing breast cancer, a number of studies have looked at soy consumption of breast cancer survivors. A meta-analysis of cohort studies showed that increased survival rates and lower cancer recurrence rates were found in women with the greatest soy consumption[76]. A 2012 study showed that of the patients who ate the most phytoestrogens post diagnosis, the 5-year survival rate was 90%, compared to 50% in those who did not consume much soy[77]. It was suggested that just a single cup of soymilk contains enough phytoestrogens to decrease recurrence risk by 25%[78]. Notably, this finding was present in women with both ER+ and ER- tumors, and was not age dependent[76].

Another hypothesis as to the mechanism of action of the protective effects of soy's isoflavones is in its ability to reactivate *BRCA* genes. *BRCA1* and *BRCA2* are known as caretaker genes, suppressing cancer and repairing DNA, which is why mutations in these genes increase the odds of developing breast cancer[79]. However, though genetics do play a role and many individuals believe that the majority of breast cancers are due to a family history, only 2.5% of cases are actually genetically linked[80]. Perhaps the reason that breast cancers seem to run in families more often than is explained by genetics, is because dietary and lifestyle habits tend to run in families. Thus, since most patients have functional *BRCA* genes, cancer in those individuals is promoted and spread through methylation, a process that suppresses gene expression and turns off the cancer regulating *BRCA* genes[81]. The mechanism by which isoflavones appear to protect against cancer growth and spread is by their ability to turn suppressed *BRCA* genes back on through demethylation, and it is estimated to take only about 1 cup of soybeans to obtain enough phytoestrogens to alter gene expression[79]. Furthermore, in addition to cancers that are *BRCA* related, soy can also benefit those with *MDM2* and *CYP1B1* genetic forms of breast cancer, and thus increased soy intake may be of benefit to women with increased genetic risk of any breast cancer, whether genetically caused or not[82].

PLANT-BASED NUTRITION AND PROSTATE CANCER

It is estimated that in 2018, approximately 1,735,350 new cases of prostate cancer will be diagnosed, 609,640 will die from the disease[83]. Additionally, based on autopsy studies, approximately 50% of men over 80 years of age die with prostate cancer, not yet knowing they had it[84]. A number of dietary components have been implicated in prostate cancer risk, and just like in breast cancer, the contributing food sources are of animal origin. For prostate cancer, this is particularly milk and eggs.

Dairy and prostate cancer

Dairy products are often advertised as "natural", yet humans are the only species who consume milk after weaning, let alone drink the milk of another species[85]. Advertising also promotes milk and other dairy as "good" for the body, yet every animal derived food product contains high levels of sex steroid hormones, especially in dairy due to the fact that milk is taken from lactating female cows[86]. Even hormone levels in so called "organic" cows have levels high enough to influence hormone related conditions including acne, reproductive dysfunction, premature puberty, and higher rates of twins[86-89]. In looking at cancer in

particular, the concern lies with the effects of growth hormones in addition to sex steroid hormones[90]. When considering that cow milk is meant to cause a calf to gain a couple hundred pounds within a few months, it makes sense that a lifetime of human exposure to those growth factors could contribute to developing cancer, and particularly hormone sensitive tumors[91,92].

The first population studies that prompted concerns linking dairy and cancer were during World War II when Japanese men were found to have a 25-fold increase incidence of prostate cancer, a finding/trend that coincided with a 7-fold, 9-fold, and 20-fold increase in egg, meat, and dairy consumption respectively[93]. Similar trends were also observed in other countries around the world at that time[94]. Numerous case control and cohort studies then confirmed that consuming cow's milk is a risk factor for prostate cancer, and additionally, that the consumption of any dairy product, not just milk, increases prostate cancer risk[95-97]. Experimental tests demonstrated that dripping even organic milk on human prostate cancer cells resulted in a more than 30% increase in cancer growth compared to a 30% suppression when almond milk was tested[92,98]. Furthermore, observational studies and animal research has indicated that in addition to cancer risk, dairy consumption may contribute to other negative health effects, including overall mortality rates[99-102].

Eggs, choline, and prostate cancer

When prostate cancer is caught early, while cancer cells are localized to the prostate gland, the 5-year survival rate is nearly 100%, yet when metastasis occurs, it can be as low as 33%[103]. Given this significant discrepancy, researchers aim to determine factors that contribute to its spread. To study dietary factors that may lead to prostate cancer progression, Harvard University researchers followed over 1000 men with early state prostate cancer for a number of years[103]. In comparison to men who rarely ate eggs, those who ate even a single egg or less per day had a 2-fold increased risk of metastasis. Even worse than eggs, was poultry, with regular consumption being linked to a 4-fold increase in risk for metastasis. One hypothesis to explain these findings has to do with HCAs, similar to that in breast cancer, which seems to build up in the muscle tissue of poultry more than other animals. Researchers determined that the substance in eggs responsible for cancer promotion, is choline, a product concentrated in eggs. Choline is converted into a toxin called trimethylamine by bacteria present in individuals who consume animal protein and is linked to higher risk of myocardial infarction, cerebrovascular events, and overall premature death[104,105]. Higher serum concentrations of choline have been linked with prostate cancer development and progression[106-108], and consuming as little as one egg every 3 days has shown to increase the risk prostate cancer mortality by about 81%[107].

Diet *vs.* exercise for prostate cancer

In 2005, Dean Ornish, a researcher well known for his studies showing that plant based diets can reverse atherosclerotic plaque lesions in heart disease, began studying the 2nd leading cause of death, cancer. Ornish created a series of experiments where he placed subjects on different diets, dripped their blood on cancer cells *in vitro*, and observed their growth rates[109]. Results showed that those randomized to the plant nutrition group has blood samples much less hospitable to cancer growth, fighting cancer 8 times better than the standard American diet. Those eating the standard American diets blood suppressed cancer cell growth by about 9%, *vs.* 70% in men who were eating plant based for a year[109]. One limitation in interpreting these results is that most lifestyle interventional studies involve changing not only diet, but exercise regimens as well. A University of California at Los Angeles team thus devised a research study comparing among 3 groups of men in order to isolate the effects of diet[25]. One group ate plant based and exercised, one just exercised while eating standard American diet, and one was a control of sedentary individuals eating the standard American diet. In the diet and exercise group, those subjects had been following a plant based diet for 14 years in addition to regular moderate exercise, whereas the exercise group consisted of those with a 15-year history of daily strenuous exercise for at least an hour per day. After dripping the blood of the participants on prostate cancer cells *in vitro*, it was found that the control groups blood killed 1%-2% of cancer cells, the exercise group killed 2000% more than controls, and the plant eaters killed 4000% more. Therefore,

results showed that exercise does play a part in cancer protection and an overall healthy lifestyle, but it cannot substitute for eating a healthy plant-based diet, and does not negate the effects of eating animal products[110].

Prostate cancer regression via nutritional intervention

In 2005 Dr. Dean Ornish studied 93 men with prostate cancer who chose not to undergo conventional therapy in order to test the effects of intensive lifestyle changes on disease progression[111]. Men were randomized into the control group who weren't given additional diet/lifestyle instructions outside of what their primary care physicians may have told them, and the experimental group were prescribed a vegan diet along with walking 30 min a day, 6 days a week[108]. Prostate cancer progression was tracked using prostate specific antigen (PSA) levels. At 1-year follow-up, control group PSA levels rose on average of 6%, whereas the plant based groups dropped by 4%, suggesting tumor shrinkage *vs.* growth. Additionally, biopsies taken pre and post dietary intervention demonstrated that the altered expression of over 500 genes, showing that changing ones' diet and lifestyle can have significant effects on gene expression[111]. At 2-year follow-up, it was found that about 10% of control group patients had to undergo radical prostatectomy due to tumor growth, whereas none of the plant-based group ended up needing surgery for cancer progression[112]. Another study in 2012 at the University of Massachusetts aimed to determine if simply reducing the ratio of animal to plant proteins would be enough to halt or reverse prostate cancer progression[113]. Subjects were randomized into 2 groups, one getting instructional classes on plant-based eating and achieving a 1:1 animal to plant protein ratio, and the other getting no dietary instructions, remaining at about a 3:1 ratio. PSA levels were analyzed, and doubling times in the plant group were lengthened from an average of 21 months to 58 months. This sounds like a very positive result, and it is, however the same effects of complete reversal that were found in previous studies of fully vegan diets, were not found in this case. Therefore, these results indicate that the safest ratio of animal to plant proteins may be 0:1.

In looking at specific plant foods that may offer particular benefits and protection against prostate cancer, soy and flaxseeds are ones to note. Just as in breast cancer, prostate cancer incidence is found to be significantly less in Asian men who tend to consume more soy products and thus more isoflavones than the typical Western/American diet[114]. Japanese and Chinese men have found to have 30 and 120 times less rates of prostate cancer than African American men respectively, partly due to higher fat intake in Western diets, but also because of soy consumption[115]. In addition to isoflavones, lignans are relevant in prostate cancer as well, and research has shown that the levels of lignans in the prostate fluid of men with low rates of cancer are higher than those with higher rates of cancer[115].

In 2001, a pilot study was conducted to determine if pre-operative consumption of flaxseed would alter PSA, hormone levels, and histopathological findings[116]. For one month prior to prostatectomy, patients consumed 3 tablespoons of flaxseed per day. Post-operative tumor analysis then showed decreased rates of cell proliferation, and increased cancer cell clearance. In addition to helping reverse existing prostate cancer, flaxseeds have also shown to prevent it from developing. In a study of men with biopsy confirmed prostatic intraepithelial neoplasia, a precancerous prostatic lesion, 15 subjects were asked to consume 3 tablespoons of flaxseed per day for the subsequent 6 months until their next scheduled biopsy. The men's PSA levels and cell-proliferation rates decreased, and 2 of the 15 men saw such a drastic decrease in their PSA levels that they did not require a 2nd biopsy[116-118]. The evidence suggests that flaxseed is a low-cost, safe nutritious food with potential to reduce the risk of prostate cancer and improve survival.

PLANT-BASED NUTRITION AND COLORECTAL CANCER

Colorectal cancer (CRC) is the third most common cancer in men and the second most common cancer in women worldwide with more than half of cases occurring in developed countries. Diet and obesity have been shown to play major roles in modulating the risk for colon cancer. Fortunately, diet is a modifiable factor and a change can be made from a disease promoting pattern to a protective pattern. While certain

individual foods have been implicated as either increasing or decreasing colon cancer risk, the overall pattern of food intake may offer the greatest influence on the development of disease. Numerous studies have shown that diets high in unrefined plant foods such as fruits, vegetables and whole grains provide protection against colon cancer while diets high in meat and saturated fat increase the risk of colon cancer. Thus, implicating vegan and vegetarian diets as potentially beneficial in preventing CRC. In the Adventist Health studies where a large prospective cohort of nearly 80,000 subjects was followed, vegetarian diets were associated with an overall lower incidence of CRC compared to non-vegetarians[119,120]. The protective effect of plant-based diets may be due in part to exclusion of meat which contains harmful substances such as saturated fats and carcinogens formed during the cooking or processing of meats. Additional protection by plant-based diets can be offered by inclusion of several beneficial plant constituents including fiber and micronutrients. Plant-based diets may also aid in weight loss or weight maintenance which may offer protection against the increased CRC risk associated with obesity. Responsible for the protective effect of vegan and vegetarian diets are plant-based foods including vegetables, fruits, whole grains, legumes, nuts and seeds[121-124]. Intake of fruits and vegetables and high fiber intake, particularly from vegetables and whole grains, has been associated with reduced risk of CRC in systematic meta-analyses and epidemiologic studies[125-130]. Fiber may help protect against CRC by reducing fecal bile acid concentrations and by being paired with micronutrients and minerals such as magnesium. A large meta-analysis including nearly 340,000 subjects found a decrease of roughly 10% in CRC risk between those consuming the most magnesium and those consuming the least magnesium[131,132]. This protective effect may be mediated by the ability of magnesium to promote DNA repair and stability of the genome[133]. Epidemiological observations have also demonstrated a decrease in the incidence of cancer when consuming a diet of plant-based foods that is rich in phytochemicals. Phytochemicals are plant metabolites that can exert a chemopreventive effect through their antioxidant properties that act to lower oxidative stress-induced DNA damage, thus protecting cells from mutations that trigger carcinogenesis. This may contribute to the protective effect of plant-based diets against colon cancer. Some phytochemicals that may offer protection include curcumin (turmeric), epigallocatechin gallate (green tea), resveratrol (grapes), phenethyl isothiocyanate, sulforaphane (cruciferous vegetables), hesperidin, quercetin and 2'-hydroxyflavanone (citrus fruits)[133]. Other protective elements in a cancer-preventive diet include selenium, probiotics, folic acid, vitamin B12, vitamin D, chlorophyll and antioxidants such as carotenoids[134].

The harmful effects of meat were perhaps first noted in an epidemiologic study supplying evidence about the association between red meat and CRC risk. A demonstration of correlation between per capita meat intake and incidence of colon cancer was shown in women from 23 countries in 1975[135]. A strong association between red and processed meats and colon cancer has since been shown in numerous studies and large meta-analyses[136-139]. Several compounds in meat are thought to be responsible for this association. These compounds include polycyclic aromatic hydrocarbons, nitrosamines, HCAs formed during cooking, and heme iron causing pro-oxidant effects[140-142]. Other factors associated with increased CRC risk are foods containing high amounts of saturated fats and cholesterol as well as high serum levels of cholesterol, oxidized low density lipoprotein and triglycerides[143-145]. In those individuals with an existing diagnosis of colon cancer, western diets have been implicated with lower survival rates[146]. In contrast, a diet lower in red and processed meats and higher in fruits, vegetables and whole grains combined with exercise and healthy body weight has been shown to prolong overall and disease-free survival rates[146].

PLANT-BASED NUTRITION AND OTHER CANCERS

Plant-based diets have also been shown to offer protection against a myriad of other GI and non-GI cancers. A systematic review and meta-analysis found a two-fold difference in gastric cancer risk among those eating a healthy diet with high fruit and vegetable content to those eating a Western diet high in meat, fats and starches[147]. Especially processed and red meat intake has been associated with increased gastric cancer risk[148] which may be partially mediated by the food preservative nitrites used in processed meats.

In contrast, plant sources of nitrates are not associated with increased gastric cancer risk[149]. Likewise, pancreatic cancer risk increases with higher intakes of red meats and animal fats while fruits, vegetables and whole grains appear to lower the risk[150-152]. A review of dietary cervical cancer prevention strategies also found a high intake of fruits and vegetables to be protective against cervical intraepithelial neoplasia. Higher serum vitamin, mineral and antioxidant concentrations were found in association with reduced risk of high-grade cervical intraepithelial neoplasia[153]. In endometrial cancer an increased risk has been noted in those consuming a Western diet high in animal products and refined carbohydrates[154] while a diet high in plant foods appears protective[155]. In another study, increased saturated fat intake in those with higher circulating estrogen was found to be the main contributing factor associated with endometrial cancer while consumption of fruits and vegetables was inversely associated with endometrial cancer risk[156]. Similarly, highest fat intake from animal products was tied to 30% increase in ovarian cancer risk when compared to those eating the lowest amount of animal fat[157]. Dietary patterns have also been shown to influence lung cancer risk. Again, diets high in meat were found to increase lung cancer risk by 35%[158] and two recent meta-analyses concluded that risk for lung cancer was greatly reduced in those consuming the most fruits and vegetables compared to those consuming the least[159,160]. The harmful effects of Western diets high in meat are likely influenced both by inclusion of damaging compounds in meat as well as exclusion of protective components in plant foods.

CONCLUSION

Diet is one of the main causes of premature death and disability in developed countries and contributes to the burden of cancers commonly encountered in Western society. Due to the strong influence of diet on cancer incidence and progression as well as the large financial burden imposed by current treatment regimens, prevention through adherence to a mainly plant-based diet presents an attractive means of combating the problem. Though there remain some misconceptions about vegan diets, particularly concerning iron and B12, The Academy of Nutrition and Dietetics' official position on plant based diets states that "appropriately planned vegetarian, including vegan, diets are healthful, nutritionally adequate, and may provide health benefits for the prevention and treatment of certain diseases including ischemic heart disease, type 2 diabetes, hypertension, certain types of cancer, and obesity"[161]. Therefore, concerns about nutritional inadequacy of vegan diets are unwarranted when diets are appropriately constructed.

Plant-based diets have also shown to be healthy and beneficial for children. The authors did not come across any studies regarding nutritional interventions for cancers in children specifically, however plant-based nutrition is associated with improved general health and prevention of chronic diseases in children as well as adults. For example, the consumption of animal-sourced protein at one year of age has shown to be positively correlated with increased body mass index and body fat by 6-7 years of age[162-164]. Excess weight in childhood is linked to many chronic disease conditions including insulin resistance, type 2 diabetes, hypertension, and cardiovascular disease[165]. Since pre-cancerous changes and development of risk factors can begin years before clinical cancer presents itself, even as early as in utero[21], and considering that habits developed in childhood often persist into adulthood, it is beneficial to develop healthy nutritional patterns at the start of life to help promote longevity and a disease free existence.

As reviewed in this article, adoption of a plant-based diet provides robust benefits against a multitude of cancers while presenting virtually no threat of unwanted side-effects. A well-planned plant-based diet is a simple and cost-effective intervention that can be used alone to prevent disease or in adjunct with conventional treatment when disease is already present. Besides offering protection against cancers, a plant-based diet has also been shown to be protective against other Western chronic diseases including diabetes, heart disease, and obesity. The current inadequacy in nutrition education and knowledge among physicians remains a barrier for more widespread prescription of diet change for cancer prevention that should be addressed starting early in medical education. With the unsustainable nature of current cancer treatment

regimens, focus on prevention, especially through diet and lifestyle changes, presents an important paradigm shift with the potential to make a marked impact on the burden of disease.

DECLARATIONS

Authors' contributions

Conception and design, administrative support: Madigan, M
Provision of study materials or patients, collection and assembly of data, data analysis and interpretation, manuscript writing, final approval of manuscript: Madigan M, Karhu E

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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