Research Article

A Study on Plant Based Dietary Patterns and Cancer Risk

Nagarathna Purada Kattimani Matada, Mukumbayi Mulumba Philippe, Raju Koneri
Department of Pharmacology, Karnataka College of Pharmacy, Bangalore, Karnataka, India.
***Corresponding author's E-mail:** nagarathna_pkm@yahoo.co.in

Accepted on: 04-10-2013; **Finalized on:** 30-11-2013.

ABSTRACT

This article reviews current evidence regarding the relationship between vegetarian eating patterns and cancer risk. Although plant-based diets including vegetarian and vegan diets are generally considered to be cancer protective, very few studies have directly addressed this question. Most large prospective observational studies show that vegetarian diets are at least modestly cancer protective (10%–12% reduction in overall cancer risk) although results for specific cancers are less clear. However, a broad body of evidence links specific plant foods such as fruits and vegetables, plant constituents such as fiber, antioxidants and other phytochemicals, and achieving and maintaining a healthy weight to reduced risk of cancer diagnosis and recurrence. Also, research links the consumption of meat, especially red and processed meats, to increased risk of several types of cancer. 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 risk of cancer.

Keywords: Cancer, Diet, Vegan, Prevention.

INTRODUCTION

Despite widespread research efforts and increasing treatment options, cancer remains a leading cause of death worldwide. In 2004, cancer accounted for 13% of deaths worldwide (~7.4 million people) with projections estimating an increase to 12 million deaths in 2030.[1] Yet cancer is still considered a largely preventable disease with estimates of up to 90%–95% of the risk with roots in environment and lifestyle.[2] Important lifestyle factors include tobacco use, diet, alcohol, sun exposure, environmental pollutants, infections, stress, obesity, and physical inactivity. Dietary factors were estimated to be responsible for 30%–35% of all cancers in the US in 1981.[3] More recent estimates keep 35% as the overall impact of suboptimal dietary choices, but more specifically note that diet may be linked to as many as 70% of cases of colorectal and prostate cancer, 50% of cases for breast, endometrial, pancreatic, and gallbladder cancers, but only to about 20% of cases of lung, bladder, mouth, and esophageal cancers.[4]

While it is clear that dietary patterns and choices are important modulators of cancer risk, the question remains just what dietary pattern is optimal for primary prevention of cancer. The question remains just what dietary pattern is optimal for primary prevention of cancer. The purpose, then, of this study is to review current evidence regarding the relationship between vegetarian eating patterns and cancer risk.

Cancer

Cancer encompasses a group of diseases related to malignant neoplasms. Known characteristics include: lack of apoptotic expulsion of mutant cells, prolific cell division with no inhibitor mechanisms; invasion of and nutrient diversion from 'normal' tissue cells, metastasis (blood and lymph) and/or tumour formation.[4] In 2007, 13% of global mortality (~7.9 million people) was attributed to cancer.[5,6] While recent reductions have occurred in affluent countries (presumed due to technological advances[6-10] and/or education), an ageing population may elevate mortality (~12 million by 2030).[5]

While cancers can arise from genetic predisposition, reduced immunity and adverse external environmental factors (pollution, toxins, etc.[13,14] most are considered preventable (e.g. ~1.5 million deaths linked to smoking).[6-10] Diet (including cooking methods and alcohol consumption, ingestion of carcinogenic-initiating or -promoting foodstuffs and exclusion of anti-carcinogenic foodstuffs) accounts for ~30% of cancers in developed countries.[5,6,10,15-17]

While some propose the tumorigenic role of diet is more 'modifying' than 'instigating'[18], the WHO's 'Global Burden of Disease' survey study[19] estimates (by way of extrapolating observational data) that increasing fruit and vegetable intake to a 600 g baseline could reduce the risk of esophageal, stomach and lung cancer by 20%, 19% and 12%, respectively. Health authorities advocate diets limited in animal-based foods, charring cooking methods, dairy products, refined sugars, salt and hydrogenated and saturated fats, and rich in a selection of plant-based foods to protect against cancer.[13,16,17,20]

This is not surprising the high quantity of non-nutritive phytochemicals (including carotenoids, polyphenols, flavenoids, isoflavones, catechins, phenolic compounds, indoles, tocotrienols and tocophenols) that plants contain possess well documented antioxidant, antineoplastic, anti-inflammatory and/or anti-carcinogenic

properties.[10,18,21-27] Elevated quantities of protective phytochemicals and fiber in vegan diets were confirmed by Dewell et al.[28], though use of soy protein supplements may have enhanced results. Steinmetz and Potter (1996)[26] conducted a journalistic review of 228 published research studies (22 of which were animal studies, whose results should be approached with caution) investigating the protective effects of vegetables and fruit (including tomatoes). They reported strong inverse correlations between high consumption and cancer (especially stomach, esophageal, lung and bladder). Conversely, a significant number of the studies indicated positive correlations between citrus fruit and breast and colon cancers, and legumes and colon cancer.

Vegan diets, however, are not defined by what they incorporate, but rather what they omit. Whereby any diet can increase protective dietary components and limit detrimental ones, on a molecular level the difference between 'limiting' and 'removing' food groups is significant. Vegans omit meat, fish and dairy, lending conjecture toward protein, calcium and B12 deficiencies and variations in essential fatty acid levels.[29,30]

DIETARY PATTERNS AND CANCER RISK

Epidemiologic evidence from the Cornell–Oxford China Study conducted in the 1970s and 1980s demonstrated important relationships between dietary patterns and cancer risk and highlighted the importance of diets rich in whole plant foods for cancer prevention.[31] The magnitude of difference in cancer risk within China ranges by more than a factor of 10 across the 65 counties studied. Campbell and colleagues found that a group of diseases (notably cancers of the colon, lung, breast, brain, as well as leukemia, cardiovascular disease, diabetes) were all associated with a diet of nutritional extravagance – meaning a diet that was associated with higher levels of blood cholesterol and blood urea nitrogen. These risk markers were directly associated with the intake of milk, meat, eggs, dietary fat, and animal protein and inversely associated with dietary fiber and legumes. In addition, breast cancer mortality increased with increasing dietary fat concentration and blood cholesterol levels. Higher blood levels of vitamin C and beta carotene, antioxidants provided by plant foods, were associated with lower rates of several cancers.[31] In another report, Campbell and Chen make the strong statement that "there appears to be no threshold of plant food enrichment or minimization of fat intake beyond which further disease prevention does not occur". And they add that in the context of diets in China the addition of small amounts of foods from animal sources is associated with increased risk of chronic degenerative diseases including cancer.[32]

Similarly, Carroll and colleagues observed a strong relationship between animal fat intake and breast cancer mortality across 38 countries and no relationship between plant fat intake and breast cancer in these same countries.[33] And in China during this time, where the variations in fat intake were mostly from animal-based foods and ranged from 6%–24% percent (all within "low-fat" ranges by US standards), breast cancer risk increased as fat intake increased.[34]

Evidence from migration studies in the 1980s also pointed to the hypothesis that plant-based dietary patterns are more cancer protective than standard Western dietary patterns that tended to be higher in animal food, sugar, and highly processed food products. For example, in one study breast cancer incidence for Japanese women who migrated to Hawaii increased nearly 3-fold in the first generation and increased to 5-fold higher in the second generation. Similarly, colorectal cancer incidence jumped 5-fold for first generation immigrants in this same study population while stomach cancer incidence dropped by about half.[35] Other migrant studies demonstrate dramatic shifts in site-specific cancer incidence when groups of people migrate to countries with different dietary and other lifestyle patterns.[36] Worldwide nutrition transitions in less developed countries continue to rapidly unfold and are linked to cancer largely through their direct or indirect effect on body weight. The key changes increasing body weight and thereby increasing the risk of cancer are foods from animal sources, caloric sweeteners, and highly energy dense beverages and foods. This evidence clearly points to the importance of environment, including food availability and dietary patterns, for cancer risk.

Current interest in diets of hunter gatherers, both past[37-40] (Palaeolithic) and present[41] (e.g. the Papua New Guinean Samberigians and Kitavans and the Australian Aboriginal tribes) is due to hypothesis that their intake of wild meat, fish and shellfish, leafy vegetables, fruit, nuts, insects and larvae[38,39] is causal of consistent findings of low relative risk (RR) for diseases such as obesity, hypertension, hyperinsulinaemia, ischaemic heart disease, stroke and malnutrition.[39] Outside the hunter-gatherer realms, significant dietary modifications from farming (meat and fish), refinement (grains, sugars, fats) and the inclusion of dairy, alcohol and salt are hypothesized to have produced ever-increasing occurrence of these maladies, thus affording them the labels 'diseases of civilization' or 'diseases of longevity'.[38]

At present, cardiovascular disease (CVD) and cancer are the most prevalent mortality causing non-communicable diseases globally.[42] Vast amounts of time, money and resources are utilized to identify risk reduction factors, many of which are fashioned after dietary aspects.

The modern diet consists of three main groups: omnivorous (consumption of all food groups); lacto-ovo-vegetarian or 'vegetarian' (consumption of all edible plant-derived material, eggs, dairy, honey; though no meat or fish) and vegan (sole consumption of edible plant-derived material). There exist variations to these (e.g. fructarian, pescatarian) as well as scope for dominance of particular food group or nutrient depending on the desired outcome (e.g. high animal protein, low refined carbohydrate, low fat, high fibre, etc).

Nutritional research has invariably found vegans to consume less zinc, protein, calcium, fat (including saturated fat), cholesterol and B12 and more carbohydrate, fibre, vitamins A, C, B6 (folate), B9, potassium, magnesium, manganese, copper and iron (presumably plant-derived non-haeme iron, whose bioavailability is inferior to haeme iron)[43-45] relative to their omnivorous and vegetarian counterparts. One study reported vegans to show more diversity in their nutrient sources and to augment their B12, calcium, zinc, selenium and vitamin D intake with supplements.[46]

Non-dietary related aspects were found to include higher socio-economic status, reduced alcohol and tobacco consumption and greater levels of education and dietary restraint (which reduced propensity toward obesity).[44, 47-49] While these factors may contribute to cancer and CVD risk reduction or promotion, only nutritional factors are investigated herein.

Dietary Factors and Cancer Risk

Red and processed meats increase the risk of some types of cancer. Diets rich in plant foods decrease the risk of many types of cancer; specifically, beneficial effects have been shown for fiber, fruits, vegetables, legumes including soy foods, and whole grains. Obesity increases the risk of some types of cancer. Many plant constituents, some nutrients, and other non nutriuent phytochemicals increase immune function. Each of these will be discussed below and each one points to the potential use fullness of vegetarian dietary patterns for reduction of cancer risk.[2, 50-59]

Meat and Cancer

Higher levels of meat, especially red meat (egg, beef, pork, lamb) and processed meat (egg, bacon, hotdogs, luncheon meat, chicken nuggets, and other salted or cured meats) have been linked to a variety of cancers in a number of studies.[2,10]

When meat is cooked at high temperatures through pan frying, grilling, or barbequing potential carcinogenic compounds, heterocyclic amines (HCAs), are formed.[60,61] These compounds and have been strongly linked with increased risk of cancer at a number of sites.[62] A study of grilled chicken dishes from popular chain restaurants in California, found that all 100 samples contained some 2-Amino-1-methyl-6-phenylimidazo(4,5-b)pyridine (one common HCA). The authors concluded that "although risks to the public have not been precisely calculated, strategies to reduce exposure to these and other carcinogens are warranted".[63] They also note that HCA formation in plant based grillable foods such as veggie burgers or mushrooms is highly unlikely.[63] By definition, vegetarian diets are meat free. Even semi vegetarian diets are usually devoid of red and processed meats. Studies linking the consumption of red meat and the consumption of HCAs to cancer risk highlight the potential benefits of vegetarian eating styles to reduction of cancer risk.

BODY WEIGHT AND CANCER

Convincing evidence links higher levels of body fatness to increased risk of cancers of the esophagus, pancreas, colorectum, breast (postmenopausally), endometrium, and kidney.[36] Consistent evidence also indicates that overweight and obesity are significant risk factors for cancer recurrence and comorbidities including cardiovascular disease and diabetes among cancer survivors.[64] Adopting a physically active lifestyle can help individuals achieve a healthy weight and has been found to reduce the risk of colon and breast cancer.[64]

Vegetarians on average weigh 3%–20% less and have lower rates of obesity than omnivores.[65] In addition, short term studies of low-fat vegetarian and vegan diets have been successfully utilized to reduce body weight.[65]

For these reasons, adopting a low fat vegetarian diet and regular physical activity will likely move individuals to a healthy weight and therefore reduce cancer risk.

DIETARY PROTEIN MODULATES GLUCAGON/INSULIN ACTIVITY

Dietary protein triggers release of both insulin and glucagon. However, the pancreatic islets obviously do not detect 'protein' per se, but rather the postprandial increase in circulating amino acids.[66-69] The mechanisms whereby pancreatic α and β cells respond to amino acids are clearly distinct, since their responses to individual amino acids differ greatly. As a rough rule of thumb, essential amino acids are relatively more effective for releasing insulin, whereas non-essential amino acids – particularly arginine and pyruvate precursors – preferentially release glucagon. This makes sense homeostatically. When essential amino acids are amply available, it is appropriate to stimulate protein synthesis and storage with an insulin burst. When the non-essential amino acids used avidly for gluconeogenesis, as well as arginine (a catalyst of the urea cycle), are present in excess, it is reasonable for increased glucagon activity to stimulate gluconeogenesis. The failure of branched-chain amino acids to trigger glucagon release is understandable in light of the fact that these amino acids are catabolized primarily in skeletal muscle, which is not responsive to glucagon.

In general, vegan proteins tend to contain a higher fraction of non-essential amino acids than the main animal-derived dietary proteins do.[70] (A notable exception is gelatin.) For this reason, it is reasonable to expect that, if total protein intake is kept invariant, a vegan diet will promote greater net glucagon activity than an omnivorous diet.

Presumably, the fasting amino acid profile is as crucial a determinant of basal glucagon secretion as fasting glucose is for insulin secretion. Conversely, even though basal plasma levels of essential amino acids may not in themselves have a potent impact on insulin secretion, they can be expected to modulate beta cell response to fasting or post-prandial glucose. Thus, when dietary

protein is relatively high in non-essential amino acids, down-regulation of insulin and up-regulation of glucagon is a logical consequence.

As compared to soy protein, casein is a relatively poor source of non-essential amino acids; it is notably low in arginine and glycine, which are excellent secretogogues for glucagon. Sanchez and colleagues demonstrated that addition of arginine and glycine to a casein-based liquid meal resulted in a substantial increase of the postprandial glucagon/insulin ratio.[71] (The fact that milk proteins are relatively poor glucagon releasers is probably not accidental – milk protein is 'intended' for the anabolic needs of the growing infant, not as substrate for gluconeogenesis).

Health Benefits of Increased Glucagon Activity

The liver appears to be the sole significant target for glucagon activity. The action of glucagon on hepatocytes is mediated by a stimulation of adenyl cyclase that raises cAMP levels.[72] Insulin acts to antagonize hepatic glucagon activity, by activating cAMP phosphodiesterases and by additional mechanisms.[73,74] Thus, the ratio of circulating glucagon to insulin is a crucial determinant of net glucagon activity in hepatocytes.

cAMP and protein kinase A regulate the synthesis of a wide range of hepatic proteins. In particular, cAMP downregulates the synthesis of a number of enzymes required for de novo lipogenesis and cholesterol synthesis (including citrate lyase, acetyl CoA carboxylase, fatty acid synthetase, and HMG-CoA reductase), while up-regulating key gluconeogenic enzymes as well as the LDL receptor and IGFBP-1.[75-85] cAMP also post-translationally modulates the phosphorylation of key hepatic enzymes to stimulate gluconeogenesis and fatty acid oxidation.[86-90]

The actions of cAMP in hepatocytes are readily rationalized when we realize that glucagon, as well as epinephrine (which likewise increases hepatocyte cAMP), are signals evoked by hypoglycemia. These hormones suppress less urgent anabolic activities of hepatocytes (such as fat or cholesterol synthesis) so that most available free energy can be diverted to fuel gluconeogenesis. Hepatic fatty acid oxidation accelerates to meet the increased energy needs for gluconeogenesis and to generate ketone bodies as ancillary fuel for the central nervous system. The induction of IGFBP-1 – a short halflife protein that sequesters unbound IGF-I, blocking its activity – is likewise physiologically adaptive. During hypoglycemia, the tonic insulin-like activity of the circulating pool of IGF-I could worsen matters by pushing serum glucose lower.[91-93] The cAMP-mediated acceleration of IGFBP-1 synthesis minimizes this problem by rapidly down-regulating IGF-I activity. Suppression of serum 'somatomedin' activity following glucagon administration has in fact been documented in human volunteers.[93] The effects of a chronic net increase in hepatic glucagon activity are readily predicted:

- ❖ a reduction in de novo lipogenesis, decreasing fat storage in animals;
- ❖ a reduction in cholesterol synthesis and in circulating LDL cholesterol
- ❖ an increase in hepatic lipid oxidation (in part owing to lower malonyl-coA levels) that, in conjunction with the decrease in lipogenesis, causes a reduction in triglyceride synthesis and in serum triglycerides;
- ❖ a decrease in effective IGF-I activity that can be expected to retard cancer development and in some instances slow cancer growth. (IGF-I, a crucial 'progression' growth factor, enhances the mitotic rate of stem cells, pre-neoplastic lesions, and some cancers, while inhibiting apoptosis.[94-98]

These effects are precisely what are observed when animals or humans are switched from omnivorous or casein-based diets to comparable diets in which soy protein is substituted for animal proteins. Soy-based diets decrease weight gain in obesity-prone rats[99], lower elevated serum LDL cholesterol in cholesterol-fed rodents and in hypercholesterolemic humans[99,100], lower elevated serum triglycerides, and often inhibit cancer induction and/or slow cancer growth in various animal cancer models.[101,102]

WEIGHT REDUCTION WITH VEGAN DIETS

since hepatic fatty acid oxidation promotes appetite control and lowers the respiratory quotient[103], a relative disinhibition of hepatic fatty acid oxidation in vegans may play a role in the body weight reduction observed during ad libitum vegan diets. Increased thermogenic activity may also be involved; glucagon has thermogenic effects that is part may reflect the uncoupled nature of hepatic ketogenesis.[104-106] Additionally, Iritani et al. recently reported that conversion of thyroxine to triiodothyronine is catalyzed more efficiently by liver microsomes derived from soy protein-fed rats (as compared to casein-fed controls); this was paralleled by significantly higher plasma T3 levels in the soy group.[99] Conveivably, this up-regulation of 5'-deiodinase activity may reflect increased growth hormone produciton[107] – a consequence of soy feeding observed clinically.[71]

Vegan diets may also impact adipocyte function. Kern et al. report that human adipocytes express IGF-I receptors, and that indeed the physiological activator of human adipocyte lipoprotein lipase activity is IGF-I rather than insulin.[108] This intriguing finding merits replication. The implication is that IGF-I has an important anabolic impact on adipocytes – very reasonable in light of IGF-I's function as a signal of abundance – and that conversely, measures (such as vegan diets) which down regulate IGF-I activity should promote leanness. Analogously, some of the weight loss on vegan regimens presumably is attributable to loss of lean mass consequent to a decreased anabolic impact of IGF-I on skeletal muscle.

Vegan Diets Vs Cancer

In a nutshell, the thesis presented here is that animal protein – precisely because it is 'high-quality' protein, rich in essential amino acids – will up-regulate IGF-I activity and thereby act as a cancer promoter; 'low-quality' vegan proteins can be expected to have the opposite effect. As stated previously, IGF-I acts as a 'progression factor' for most normal and pre-neoplastic tissues; although often not sufficient to induce mitosis by itself, IGF-I usually works in tandem with 'competence' growth factors to promote cell turnover.[95] Induction of the IGF-I receptor is often one of the essential roles of competence growth factors. Recent studies also show that IGF-I can inhibit apoptosis in many normal and neoplastic cell lines.[97,98,109] It is now believed that apoptosis of genetically damaged cells is crucial to cancer prevention; cancer promotional agents invariably demonstrate anti-apoptotic activity.[110-115] Increased IGF-I activity can be expected to increase the rate at which fixed mutations are accumulated in stem cells by promoting stem cell turnover; by suppressing apoptosis, it can be expected to increase the chance that initiated cells will engender clinical cancer. In addition, the mitotic and apoptotic rates of many cancers are sensitive to IGF-I activity.[95] Dietary modulation of IGF-I activity can therefore be expected to have profound consequences for cancer risk and progression.

As noted above, reduction of IGF-I activity during a vegan diet can be expected owing to up-regulation of IGFBP-1. However, the possibility that such diets may also modestly decrease hepatocyte synthesis of IGF-I should be considered. In clinical or animal studies, low-protein diets of adequate caloric content decrease the serum level and hepatic synthesis of IGF-I[116-120]; this effect appears to be attributable to a dietary deficit of certain essential amino acids.[120-122] Low intake of these essential amino acids markedly destabilizes the 7.5kb form of the IGF-I mRNA, and may also impede translation of IGF-I mRNAs.[122-124] Severe protein restriction may not be required to evoke this effect.

Moreover, down-regulation of IGF-I activity in vegans is often not solely attributable to the protein content of vegan diets. To the extent that vegan diets, as compared to omnivorous diets, tend to be relatively low in fat (especially saturated fat), and high in fiber, these factors should promote increased insulin sensitivity – both acutely, and by aiding prevention of obesity.[125,126] This improved insulin sensitivity will down-regulate insulin secretion, thus contributing to the protective increase in glucagon/ insulin ratio and the resulting up-regulation of IGFBP-1. Evidently, several independent mechanisms can interact to reduce IGF-I activity in vegans. (Perversely, the saturated fats featured in many animal products are the most efficient at inducing insulin resistance, whereas ingestion of monounsaturates – found in such favorite vegan foods as avocadoes, olives, and olive oil – appear to have little impact on insulin sensitivity in humans[127,128]; perhaps this is a major reason why monosaturates emerge blameless in much recent epidemiology.)

Hyperinsulinemia as A Risk Factor For Breast, Endometrial, And Colon Cancers

Several authors have presented cogent evidence that hyperinsulinemic insulin resistance is an important risk factor for postmenopausal breast cancer, and that hyperinsulinemia induces the increased testosterone production, the reduction in serum SHBG, and the increased free estradiol levels that characterize subjects at high risk for this disorder.[129-132] It may be reasonable to extend and clarify this hypothesis by proposing that the fundamental risk factor is a high activity of insulin relative to glucagon in hepatocytes, resulting in a suppression of IGFBP-1 production. As suggested previously[130-132], the consequent increase in effective IGF-I activity can be expected to potentiate the LH-induced production of androgens by ovarian stroma,[133-135] while decreasing hepatic production of SHBG. Peripheral aromatization of these androgens will give rise to estrogens, an increased proportion of which will remain unbound owing to the decrease of circulating SHBG and the increased competition by testosterone for binding to this SHBG. The increased effective activities of both estrogen and IGF-I will then synergize to stimulate mitosis and inhibit apoptosis in pre-neoplastic breast tissue; this synergism results, at least in part, from estrogen-mediated induction of IGF-Ireceptors.[136,137]

This formulation recognizes a countervailing protective role for glucagon – and, by implication, for vegan proteins that preferentially promote glucagon release. It also stresses the importance of insulin *activity* on hepatocytes. The equivocal impact of diabetes on breast cancer risk[132] is rationalized by the realization that net insulin activity on hepatocytes is *decreased* in diabetics – even in type 2 diabetics who are hyperinsulinemic. Hepatocytes are typically insulin resistant in type 2 diabetics; in type 1 diabetics and in type 2 diabetic with profound beta cell failure, portal insulin concentrations are sub-normal. That some studies nevertheless do see an increased breast cancer risk associated with type 2 diabetes[138,139] may reflect the fact that this type of diabetes is usually preceded by a long period of compensated hyperinsulinemic insulin resistance.

These considerations enable the prediction that a low fat vegan diet will be profoundly protective with respect to risk for postmenopausal breast cancer. The protein content of this diet will preferentially support glucagon activity and possibly decrease IGF-I synthesis. Other aspects of the diet – a low intake of fat, increased fiber, decreased propensity to induce obesity – will promote good peripheral insulin sensitivity and thus down regulate insulin secretion. Such diets are likely to be relatively high in phytochemicals that may have anti-initiating activity, and the possibility that phytoestrogens contribute some protection does merit further evaluation.[140]

Endometrial cancer is also associated with obesity (and, by implication, insulin resistance), and the role of increased unopposed estrogen activity in its etiology is

well known. A favorable impact of a low-fat vegan diet on endometrial cancer risk is therefore readily predicted. As in the breast, estrogen induces IGF-I receptor expression in the uterus.[141]

Risk of colon cancer has likewise been linked to hyperinsulinemia.[142] That induction of this cancer may be particularly sensitive to IGF-I activity is suggested by the high-incidences of colon polyps and colon cancer associated with acromegaly.[143,144] The normal colonic mucosa, as well as many colon adenocarcinomas, are IGF-I sensitive.[145-149]

The puzzling fact that postmenopausal estrogen replacement does not increase breast cancer risk as greatly or consistently as might be expected, may reflect the fact that orally-administered estrogens (but not transdermal or endogenous estrogens) suppress hepatic production of IGF-I.[150] This suggests that long-term estrogen replacement therapy may reduce the risk of colon cancer and perhaps of other cancers that are not estrogen-dependent. In fact, decreased colon cancer risk associated with estrogen replacement has recently been demonstrated,[151-155] this effect is quite substantial – 30–50% reduction in risk is seen in current or long-term users.

A concurrent vegan diet and insulin-sensitizing lifestyle should amplify this benefit, and also reduce the breast cancer risk associated with estrogen replacement. Indeed, the down-regulation of IGF-I activity achievable by oral estrogen in conjunction with a vegan diet might be sufficiently large to be useful in cancer therapy – either as a palliative regimen or as an adjuvant to apoptosis-inducing measures. Tamoxifen, which is reported to decrease IGF-I and/or up-regulate IGFBP-1[156,157], might be a useful alternative to estrogen in men or in women who have estrogen-sensitive tumors. It will be interesting to determine whether soy phytoestrogens can influence hepatic IGF-I production. In light of the media frenzy regarding hormone replacement therapy's impact on breast cancer risk, wouldn't it be ironic if such therapy proves to have a neutral or even favorable impact on *overall* cancer mortality?

Igf-I Activity and Prostate Cancer Risk

IGF-I is a potent growth factor for normal prostatic epithelium, as well as for prostate adenocarcinoma cell lines[158-164]. That IGF-I activity is crucial for prostate cancer growth is suggested by studies showing that IGFBP-1 and other IGF-1 antagonists suppress the proliferation of cultured prostate cancer cells, that transfection of such cells with antisense DNA to the IGF-I receptor inhibits their growth and invasiveness in vivo, and that an antagonist of GHRH (which decreases IGF-I levels) suppresses the growth of human prostate cancer cell lines in nude mice.[163-167] Prostate-specific antigen (PSA), a marker for prostate cancer prognosis, is a serine protease that cleaves and inactivates IGFBP-3; it may therefore serve to induce a local increase in IGF-I activity.[168] There is evidence that IGF-I may activate the androgen receptor in human prostate cancer cell lines, in the *absence* of androgens.[169,170]

Increased IGF-I activity can also up-regulate testosterone availability. In addition to suppressing hepatic SHBG production, IGF-I may promote GnRH secretion, potentiate the LH response to GnRH in pituitary gonadotrophs, and likewise potentiate the steroidogenic response of Leydig cells to LH.[171-176] Reduced levels of free testosterone reported in vegetarians may reflect these effects.[177,178] It can be concluded that high IGFI activity should have a potent growth promotional/antiapoptotic impact on prostate epithelium, owing both to a direct impact of IGF-I, as well as an increase in testosterone availability.

Two other high-incidence cancers in Western society are those of the ovary and pancreas. Both theca and granulosa cells of the normal ovary are IGF-I responsive.[133-135,179] Virtually all ovarian cancers and cancer cell lines examined express IGF-I receptors, and respond to IGF-I as a growth factor.[180,181] Estradiol potentiates the response to IGF-I in some ovarian cancer cell lines by up-regulating the IGF-I receptor.[182] Case-control studies often but not invariably point to obesity as a risk factor.[183-186] With regard to the pancreas, IGF-I appears to be a progression factor for cells of the exocrine pancreas, and many recent reports indicate that pancreatic adenocarcinomas express IGF-I receptors and are IGF-I responsive.[187-190] In some pancreatic cancer cell lines, IGF-I functions as an autocrine growth factor, such that antibodies to the IGF-I receptor, or antisense DNA to this receptor, inhibit cell growth in vitro. An LHRH agonist, which down-regulates IGF-I receptor expression in carcinogen-induced autogenous pancreatic cancers in hamsters, markedly retards the growth of these cancers.[191] Some epidemiology links pancreatic cancer risk to high BMI as well as to diabetes; the latter correlation, however, declines with time, suggesting that the associated diabetes is sometimes caused by the nascent pancreatic cancer. Overall, these findings appear consistent with the possibility that IGF-I activity modulates the promotion and progression of both ovarian and pancreatic cancer.[192-196]

CHEMOPREVETION OF CANCER BY PLANT POLYPHENOLS

Epigallocatechin galate

EGCG induces apoptosis and cell cycle arrest, and exhibits anti-angiogenic and anti-metastatic potential in hepatoma cells by modulating signal transduction pathways. Paradoxically, EGCG may exert its cytostatic effects against cancer cells through a pro-oxidant activity[197], although it has strong antioxidant properties. In addition, a number of animal studies have shown that EGCG prevents chemical-induced HCC. Moreover, a number of studies with tea extracts rich in EGCG have given very promising results for its chemopreventive activity[198-202], although there was not always an apparent relationship between EGCG concentration and liver tumor response.[203] So far, there are no clinical or

epidemiological studies available on EGCG chemopreventive activity against HCC. However, use of EGCG in clinical trials for other cancer types, such as cervical cancer, has given optimistic results.[203]

Quercetin

Quercetin seems to exert its chemoprevention potential through inhibition and induction of survival and death signaling pathways respectively in liver cancer cells. Moreover, in animal studies, quercetin protects from DEN- or AFB(1)-induced liver carcinogenesis due mainly to its strong antioxidant activity and consequent prevention of ROS-induced DNA mutations in critical genes for cell cycle control, such as p53. Although there are concerns about the toxicity and safety of quercetin, human studies have not shown adverse effects associated with the oral administration of quercetin in a single dose of up to 4 g or after one month of 500 mg twice daily.[204]

Luteolin

the mechanisms for the potential anticarcinogenic effects of luteolin against HCC include mainly induction of apoptosis and cell cycle arrest by action on critical molecular targets for cell survival such as p53, p21, cyclin dependent kinases and caspases in liver cancer cells.[205] Indeed, the induction of caspase-8 and -9 suggests that luteolin may activate both molecular pathways for capsases, the extrinsic and mitochondrial respectively. Moreover, like other polyphenols, luteolin's apoptosis induction in cell culture studies seems to be mediated through pro-oxidant effects.[206] There are limited data regarding the in vivo chemopreventive activity of luteolin against HCC, and thus to fully elucidate the molecular mechanisms of its action and potential use in clinical trials, more in-depth animal studies are needed.

Silymarin and Silibinin

The potential use of silymarin and its most active constituent, silibinin, as chemopreventive agents against HCC is based on their capability to induce pro-apoptotic and reduce anti-apoptotic proteins in hepatoma cells. In addition, they have been shown to possess anti-metastatic and anti-angiogenic potential in cell culture studies. Moreover, their pro-apoptotic effects on liver cancer cells have been confirmed in in vivo experiments. Interestingly, a number of clinical studies have been performed with silymarin investigating its hepatoprotective activity.[207]

Acacetine

Acacetin inhibited cell growth, induced cell cycle arrest at G1 phase and apoptosis through increase in levels of p53 protein and its downstream pro-apoptotic targets, p21/WAFI and Bax proteins. In addition, the acacetin-induced increase in Fas/APO-1 and its ligand FASL suggested the involvement of FAS/FASL system in the observed apoptosis.[208]

Genistein

Genistein induces inhibition in hepatoma cells growth, apoptosis and metastasis by modulating the expression of antiapoptotic, pro-apoptotic and regulating motility proteins, as well as the activity of cyclin dependent kinases regulating cell cycle. These in vitro effects have also been confirmed in animal studies, since genistein induced apoptosis and inhibited metastasis of HCC induced by either chemicals or implanted hepatoma cells.[209]

Daidzein

Daidzein inhibit hepatoma (i.e. HepG2, Hep3B, Huh7, PLC and HA22T) cell growth, induce apoptosis through caspase-3 activation and PARP cleavage.[210] Daidzein was also demonstrated to affect the redox status in hepatoma cells although the data are conflicting since it induced mRNA catalase expression but at the same time caused a mild oxidative stress.[211] However, an in vivo study showed that daidzein administration (50 mg/kg) to rats increased antioxidant enzymes activity such as SOD, catalase, GPx, GST, DT-diaphorase (DTD) and GSH levels in liver.[212]

Stilbenes (trans-resveratrol)

The anticarcinogenic effects of trans-resveratrol against HCC include apoptosis and cell cycle arrest by modulation of the expression and activity of pro-apoptotic, anti-apoptotic and cell cycle regulating proteins, and anti-metastatic potential and anti-angiogenic potential by modulation of the expression of pro-angiogenic molecules.[210,213,214]

Cucurmin

Curcumin's suppression against HCC cells is largely due to inhibition of abnormal cell proliferation and apoptosis through modulation of relevant signaling pathways.[202,215-217]. Curcumin has also been shown in vivo to inhibit HCC induced by chemicals or implanted hepatoma cells. Moreover, both in vitro and in vivo studies exhibited anti-angiogenic and anti-metastatic properties of curcumin against hepatocarcinogenesis.

Cafeic acid

Both in vitro and in vivo studies have shown that cafeic acid and its derivative, cafeic acid phenyl ester (CAPE), inhibit growth and metastasis of HCC through modulation of expression of proteins involved mainly in NF-jB molecular pathway.[218,219]

Protocatechuic acid

Protocatechuic acid has been shown to inhibit HepG2 cell growth through induction of JNK and p38 proteins.[220] Protocatechuic acid to induces apoptosis through mitochondrial membrane disruption and caspase-3 and -8 activation, exhibit anti-metastatic potential by reducing intercellular adhesion molecule (ICAM)-1 level, and possible anti-angiogenic and anti-inflamatory activity by reducing VEGF, interleukin (IL)-6 and (IL)-8 levels.[221]

Capsaisin

In vitro studies have shown capsaicin to induce apoptosis in HepG2 cells.[222,223] In particular, capsaicin-induced apoptosis in HepG2 cells is associated with increased levels of ROS, intracellular Ca2+, p53 protein, cytochrome c protein, an indicator of mitochondrial membrane disruption, growth arrest and DNA damage-inducible 153 (GADD153) protein, and caspase-3 activity, and decreased levels of the anti-apoptotic proteins Bcl-2 and Bax.[224]

Another study suggested that the capsaicin- induced inhibition of NAD(P)H:quinone oxidoreductase (NQO1) enzyme activity leads to increased ROS levels in HepG2 cells[225]. The increased ROS levels, in turn, result in activation of Akt and increased nuclear translocation of NF-E2- related factor (Nrf2) that binds to the antioxidant response element (ARE), thus causing the expression of heme oxygenase-1 (HO-1), an enzyme conferring cytoprotection against oxidative stress.[225]

Also, capsaicin has been shown to induce apoptosis in SK-Hep-1 HCC cells mediated through down-regulation of anti-apoptotic Bcl-2 protein and upregulation of pro-apoptotic protein Bax and caspase-3.[222]

DISCUSSION

The complexity of factors impacting overall cancer risk, the heterogeneity of cancer etiology, and the limitations and the variation in dietary patterns may be responsible in part for the lack of clarity regarding the relationship between overall cancer risk and specific dietary factors. In addition, specific constituents in these whole foods such as soluble fiber, carotenoids, indoles, isoflavones, among hundreds of others have been linked to protection against specific cancers.

Vegetarian and vegan diets tend to be higher in these protective plant foods and plant constituents than omnivorous diets. Vegetarian and other diets built mainly from plant foods would also be expected to support higher immune function, largely because they tend to be richer in cancer protective phytochemicals. The extent to which a vegetarian diet is cancer protective likely depends on how rich the dietary pattern is in these protective whole plant foods.

Wide homogeneity of vegetarian diets exists such that individuals choosing self reported vegetarian diets may exclude only some types of meat to all animal products, may include very large or very small amounts of highly processed food, may include only raw foods, or may vary widely with respect to cheese and other dairy product consumption.

Some factors may even be protective for some types of cancer and causal or promoting for other types of cancer. For example, adequate vitamin D status is thought to be protective against prostate cancer, but sun exposure (the stimulus for vitamin D production in the human body) is a major risk factor for skin cancer. Similarly higher calcium intakes are associated with decreased risk of colon cancer but increased risk of prostate cancer. Perhaps even more problematic for nutrition and cancer research generally and the question at hand specifically are the problems inherent in measuring food intake and quantifying dietary patterns.

Results for specific cancers are less clear although there is some observational evidence that vegetarian diets may reduce risk of prostate, breast, colon, stomach cancer, bladder cancer, ovarian cancer, and cancers of the lymphatic and hematopoietic tissues.

Choosing a vegetarian dietary pattern is an easy way to follow the expert recommendations to “eat mostly foods of plant origin” and “limit intake of red meat and avoid processed meat” to reduce cancer risk.

The vegan diet typically differs from vegetarian and/or omnivorous by: reduced protein, energy, saturated fat, cholesterol, calcium, B12, phosphorous, zinc and sodium levels; and increased carbohydrate, fiber, saturated fat; vitamins A, C, B6, B9, magnesium and potassium levels. Whilst aspects of this diet in reducing risk of cancer may be obvious (e.g. increased phytochemicals), studies assessing the efficacy or detriment of some nutrients remain ambiguous and/or incomplete.

A vegan diet, aside from its deficit of vitamin B12 activity (readily compensated by supplementation), is typically more micronutrient-dense (per calorie) than the diets favored by omnivores, higher in protective phytochemicals and fiber, and usually somewhat lower in fat – especially saturated fat. Fears that a vegan diet may be inadequate in protein quality or quantity are unfounded. Advocates of veganism often cite the remarkable fact that human breast milk – presumably ‘designed’ to promote anabolism during a time of rapid growth – has a protein content that corresponds to only 5% of total calories. With the exception of fruit or refined sugar or oils, the protein content of vegan foods is considerably higher than this.

Clearly, vegan protein is not the only way to achieve a favorable balance of glucagon/insulin activity. Measures which promote the insulin sensitivity of skeletal muscle, and thus down-regulate insulin secretion, should have comparable benefit. A low-fat, fiber-rich diet, coupled with regular exercise and avoidance of visceral obesity, should be useful in this regard.

CONCLUSION

No diet or regimen can be expected to be free of *any* drawback. The fact that a low-fat, fiber-rich vegan diet is likely to reduce risk for most types of cancer, should be sufficient to recommend it. Those who are willing to make less striking changes in their lifestyle can be encouraged to reduce their consumption of animal products.

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Source of Support: Nil, **Conflict of Interest:** None.