The Rationale for a Role for Diet and Nutrition in the Prevention and Treatment of Cancer (Full Text)

Jean Logan[1*] and Megan W. Bourassa[2]

1. Center for Advanced Imaging Innovation and Research (CAI2R)
Bernard and Irene Schwartz Center for Biomedical Imaging,
Department of Radiology,
New York University School of Medicine,
660 First Ave
New York, New York 10016, USA
212-263-4862
Jean.logan@nyumc.org

2. Sackler Institute for Nutrition Science
The New York Academy of Sciences
250 Greenwich St
New York, New York 10007
Mbourassa@nyas.org

*Corresponding author

Conflicts of interest: None declared

Abstract

There is considerable evidence to support dietary recommendations for prevention of cancer as well as for patients undergoing or recovering from cancer treatment. We consider here implications from human, animal and in vitro studies of the effects of dietary factors (macronutrients and micronutrients-phytochemicals) on cancer. An important epidemiology study, the China Project found a significant correlation between disease incidence (cancer, cardiovascular disease, diabetes) and markers of animal product consumption. Evidence of the role of animal protein in the promotion of cancer also comes from animal studies. Food restriction as in some form of fasting has been shown in human and animal studies to slow cancer progression. Phytochemicals from whole plant foods are protective against oxidative stress, inhibit cell proliferation, induce cell-cycle arrest, and apoptosis, act as antiangiogenesis factors and inhibit COX-2, which has been related to metastasis. Some mechanisms that mediate the effect of diet on cancer involve cell signaling through insulin factors and mTOR, a nutrient sensing complex related to growth, altered gene expression through epigenetics, and the effects of microbial metabolites produced by the gut microbiota which is strongly influenced by dietary factors. The evidence that has been accumulating for many years indicates that diet, what we eat every day, can affect disease. Besides preventing the development of cancer, it seems that this could also be harnessed to positively influence cancer treatment outcomes as well as prevention of recurrence. Since research strategies developed for drug studies are not appropriate, it is important that new methodologies be developed to study these effects.

Keywords: Cancer, nutrition, phytochemicals, dietary restriction

Introduction

Advances are continually being made in imaging technology and applied to cancer diagnosis and monitoring. Coupled with the Precision Medicine Initiative, which aims to select therapies most appropriate for individual patients, these technologies offer the possibility of early diagnosis and improved survival. However as exciting as these advances are, they do not address the fact that a large percentage of cancer occurrences are affected by extrinsic (lifestyle) factors (Wu et al., 2016). In the case of cardiovascular disease, Dean Ornish et al. (1990), C. Esselstyn (1999) and others have established that diet and lifestyle changes can prevent progression and even reverse cardiovascular disease. Ornish et al. have also taken on prostate cancer showing that intensive lifestyle changes resulted in significant decreases in serum prostate-specific antigen (PSA) after one year and after two years the same group found that 5% of lifestyle subjects compared to 27% of controls required conventional prostate treatment (Ornish et al., 2005, Frattaroli et al., 2008). Fontana et al. (2006) report that a low protein low calorie diet and exercise training are associated with low plasma growth factors linked to an increased risk of cancer. Evidence from other studies suggests that the most important lifestyle factor is diet (Barnard et al., 2003).

Much of the early work relating diet and cancer concentrated on the intake of macronutrients. Macronutrients consist of protein, carbohydrates (including fiber) and fats (including saturated fat, unsaturated fat, cholesterol) and are necessary for energy and structure. In particular fat intake has been the focus of a number of studies. Micronutrients (such as phytochemicals) make up the other dietary category and include vitamins, minerals, antioxidants and other molecules that support metabolic function. Clues concerning the impact of macronutrients upon cancer risk can be found in studies of subjects following vegetarian or vegan diets, which reduce or eliminate

consumption of animal products (composed primarily of protein and fat). Direct and indirect evidence that vegetarian diets reduce risk of cancer has been reported in a review in 2010 (Lanou and Svenson, 2010). A recent meta-analysis of observational studies found that vegan diets conferred a significant reduced risk of incidence from total cancer (Dinu et al., 2016). In addition to a reduction in animal products, these diets most likely represent an increase in micronutrient consumption via an increase in fruit and vegetable consumption. Here we consider the possibility that diet – limiting animal products, consuming a variety of whole plant foods (the main source of micronutrients) and practicing some form of limited fasting or time restricted eating can influence cancer development. Some of the mechanisms by which diet is thought to interact with cancer are discussed.

Epidemiology and Clinical Studies related to Macronutrients

Clinical studies have demonstrated that a whole food, low fat diet (allowing a small amount of animal protein) coupled with exercise decreased plasma levels of insulin-like growth factor 1 (IGF-1) and serum from subjects following this regimen reduced growth in prostate cancer cell lines (Ngo et al., 2002, Tymchuk et al., 2001). IGF-1 is a major regulator of cell growth and increased concentrations are associated with increased risk of breast, colon, lung and prostate cancer (Pollak et al., 2004). Other studies support an association between cancer and intake of animal products. A retrospective study of pancreatic cancer found higher survival associated with diet modifications, which included increased vegetables and whole grains and lower animal protein (Carter et al., 1993). A more recent study conducted by the National Institutes of health (NIH-AARP) found dietary fat from animal products was associated with an increased risk of pancreatic cancer (Thiébaut et al., 2009).

Early epidemiology studies also provide clues concerning the relationship between diet and disease. Post-war Japanese had age-adjusted mortality from common cancers 5 to 10 fold lower than in the U.S. at the same time (McCarty, 2014). Their diet at the time was quasi-vegan with 6% of total calories from animal products. However as the "Western" diet is adopted by more countries, the incidence of cancer in these countries is increasing. The findings from a study conducted in China in the 70's and 80's (The China Project) a joint collaboration between Cornell, Oxford, and Beijing University led by T. Colin Campbell, Junshi Chen and Richard Peto found associations between diet and cancer as well as other diseases (Campbell and Junshi, 1994, Campbell et al., 1998). This exploration began as a result of a massive survey done by the Chinese in the 70's, which indicated that certain cancers were confined to certain geographical locations (rates ranged by more than 10 fold from highest to lowest) suggesting that diet and environment rather than genes were responsible. A major finding from the study was that cancer, diabetes and heart disease were correlated with plasma cholesterol concentration and blood urea nitrogen, which are correlated with intake of animal protein and fat and inversely correlated with intake of vegetables (Campbell et al., 1998). Even within the range of the relatively low consumption of animal products, small increases in meat consumption were associated with increases in cancer, diabetes and heart disease (Campbell, 2014).

In another study an increase in mortality rates of cancers of the breast, prostate and colon in East Asian countries in the 2000s was observed (Zhang et al., 2012). This increase follows a shift in the last several decades from diets based on vegetable foods to diets high in animal foods and saturated fats (Popkin and Du, 2003).

Further evidence of the connection between diet and disease comes from numerous studies finding increased rates of cancer in immigrants to the US compared to rates in the native countries. For Japanese migrants to Hawaii and California, breast cancer incidence rates doubled in the first generation compared to rates in Japan at the same time (Kolonel et al., 1980). Japanese migrants also experienced substantial increases in colon cancer compared to the incidence in Japan which was 25% of that of the Hawaiian population while that of first generation migrants was the same as that of the Hawaiian population (Kolonel et al., 1980, Kolonel and Wilkins, 2006). A review and discussion of migrant studies can be found in Kolonel and Wilkins (2006).

More recently cancer incidence in vegetarians was investigated using a pooled analysis of two prospective studies in the UK, the Oxford Vegetarian Study and the EPIC-Oxford (Key et al., 2009) . Subjects were grouped according to whether they did not eat meat or fish (vegetarian), did not eat meat but did eat fish (fish eaters) and meat eaters (61,566 subjects, 32403 meat eaters, 8562 fish eaters and 20600 vegetarians). Dairy consumption was not controlled. Vegans, who also do not eat dairy, had too few cancers for analysis and were included with vegetarians. Results were controlled for smoking, alcohol, body mass index and physical activity. Stomach cancer risk was significantly lower for vegetarians than meat eaters, ovarian and bladder cancer risk was lower in fish eaters and vegetarians than meat eaters. For non-Hodgkin's lymphoma and multiple myeloma the risk was lower in vegetarians than meat eaters.

A recent meta-analysis of eighty-six cross-sectional and ten cohort prospective studies assessed vegetarian and vegan diets with respect to risk factors for chronic diseases, incidence and mortality from cardio-cerebrovascular disease, total and specific cancers (Dinu et al., 2016). A

vegetarian diet was found to confer a significant protection with respect to total cancer (-8%), and the vegan diet was associated with a significant reduced risk (-15%) of incidence from total cancer.

In the 1970's and 1980's, dietary fat and its relation to disease became a focus of nutrition committees. The McGovern committee (the United States Senate Select Committee on Nutrition and Human Needs) held hearings on the relationship between fat intake and heart disease recommending a reduction in fat intake to 35% of calories to reduce cardiovascular disease. A second committee (The National Academy of Sciences, United States) looked at the relationship between fat intake and cancer risk also recommending consumption of lower fat foods. This was supported by the observation of a positive correlation of breast cancer with total fat intake across countries with Japan, Thailand and the Philippines having low risk with average consumption less than 40g/day compared to the U.S., Denmark and the Netherlands with more than 150g/day (Carroll et al., 1986). However if the data is separated into animal versus plant fat, the correlation only holds for animal fat intake (Carroll, 1975). The Harvard Nurses' Health Study incorporated a dietary fat component in 1984, the hypothesis being that lower fat intake would be associated with a lower rate of breast cancer, implicitly assuming that dietary fat is an independent and major cause of breast cancer. The major finding from the study (89,494 subjects) was that a decrease of fat from 50% of calories to 25-30% was not associated with a decrease in breast cancer rate (Willett et al., 1992).

The Women's Health Initiative Randomized Controlled Dietary Modification Trial was a primary prevention trial of 48,835 postmenopausal women without breast cancer. The goal was to reduce fat intake to 20% of calories and increase fruit and vegetable consumption to 5 servings/day. The intervention group reduced fat intake from 38% to 24% (in year 1) of total calories, but this

occurred with an increase in protein (but a decrease in fat intake from meat) and an increase in vegetable consumption by only 1 serving/day (Patterson et al., 2003). After 8 years the intervention group had a slightly reduced (but not significant) risk of invasive breast cancer (Prentice et al., 2006). Some evidence of a greater risk reduction was seen among women with the highest fat intake at baseline. A confounding factor is the dietary changes used to achieve the lower fat. Lower fat meats (for example skinless chicken breast) contain protein and significant levels of cholesterol, which can both be related to cancer thus potentially negating the benefit of reduced fat. That cholesterol is a potential factor in breast cancer development is reviewed by Danilo and Frank (2012). A study of the relationship between total cholesterol and breast cancer found that women with high total cholesterol had a greater risk than women with low plasma levels (below 160 mg/dL) (Kitahara et al., 2011). Also increased breast cancer risk was found in women consuming elevated levels of cholesterol (Hu et al., 2012). Laboratory models are more definitive. A high fat, high cholesterol diet fed to a mouse model of breast cancer resulted in larger more advanced tumors than control animals (Llaverias et al., 2011). An association of cholesterol and cholesterol esters with breast and other cancers is discussed in a review by Antalis and Buhman (2012).

Two studies tested the effects of dietary change on breast cancer recurrence. The Women's Intervention Nutrition Study (WINS), a randomized trial (n=2,437) to determine the effect of fat intake on recurrence of breast cancer produced a statistically significantly reduction in dietary fat (29% to 20.3% of total calories from fat) and overall fewer deaths in the intervention group, but the difference was borderline statistically significant. However, further analyses suggested a stronger effect in estrogen receptor negative (ER-) cancers (Chlebowski et al., 2006). A second study of women with early stage breast cancer, The Women's Healthy Eating and Living (WHEL),

targeted increased vegetable and fruit consumption, dietary fat remained the same between baseline and intervention (n=2,448). Animal products were not controlled. No reduction in additional breast cancer events or mortality was observed in the intervention group during a 7-year follow up period (Pierce et al., 2007).

Although calories from dietary fat were reduced in some studies, the percentage is still considerably above that observed in areas with low breast cancer risk (11-15%). Also animal studies have shown a link between intake of animal foods and cancer (Armstrong and Doll, 1975, Campbell, 2014, Youngman and Campbell, 1991, Fontana et al., 2013). In none of the intervention studies was animal based food controlled, which may be responsible for the lack of effect on primary breast cancer or breast cancer recurrence. Even though the WHEL study did not show a positive effect of fruit and vegetable consumption, recent studies show plant-based diets to be protective (Dinu et al., 2016). The decreased cancer risk (for four cancers) in the UK prospective vegetarian studies suggests a role for meat in the incidence of cancer, but the lack of control for dairy is a significant drawback given the cancer promoting effects of casein in animal studies (Youngman and Campbell, 1991). A meta-analysis found that cruciferous vegetable consumption was related to a decreased risk of renal cell carcinoma in seven case-control studies but not in three cohort studies but other aspects of diet were not controlled (Liu et al., 2013). The dramatic increase (over 100%) in breast cancer deaths in Japan, China and Korea from 1975 to the present has occurred with the adoption of a “Western” lifestyle particularly diets with a high intake of animal foods. Although this does not prove a cause-effect relationship it is suggestive (Chlebowski, 2013).

Fiber, another macronutrient, was not found to be protective against cancer in a report published in 1982 by the National Academy of Sciences working group on nutrition and cancer (United States); however, recent meta-analysis studies suggest positive effects of high fiber and whole grain intake on colorectal cancer (CRC)(Aune et al., 2011). Data from the China Study also found that the highest fiber diets were associated with lower rates of CRC (Campbell and Junshi, 1994). In a report published in 1971, the very low rate of CRC in Africans (the incidence of colon cancer in the US was on the order of ten times that in Africa) was attributed to the high fiber content of the diet (Burkitt, 1971). However the diets of Africans have changed in recent years away from high fiber intake, but the incidence of CRC is still low in native Africans compared to African Americans (AA) (O'Keefe et al., 2007). Similar markers for CRC risk were found in Caucasian Americans and AA implicating environmental factors rather than genetic factors although some forms appear to be heritable. The connection between diet and CRC is thought to be mediated by microbial metabolites produced by the gut microbiota, and the composition of the gut microbiota is strongly influenced by dietary factors (Louis et al., 2014). Although the diet of the Africans changed from high fiber to resistant starch, they still ate few animal products. High meat intake has been associated with increased occurrences of CRC (Potter et al., 1993). This is thought to be related to the production of endogenous carcinogens such as N-nitroso compounds by resident bacteria. Using three controlled diets that varied in the amount of meat and resistant starch, the amount of N-nitroso compounds in feces was determined (Silvester et al., 1997). The findings from this study were that the presence of N-nitroso compounds increased with increased meat consumption. The addition of resistant starch had little effect on overall N-nitroso compounds when added to a high meat diet.

Mechanisms (macronutrients)

Protein

How diet relates to cancer incidence has been explored through experimental research in rodents. Early work in the 1990's demonstrated a link between the percentage of calories in the diet allocated to protein and incidence of cancer in rats exposed to the carcinogen aflatoxin (Youngman and Campbell, 1992, Youngman and Campbell, 1991). This research grew out of an observation of the association of primary liver cancer and animal protein consumption in Filipino children, and a report published in 1968 that aflatoxin induced hepatocarcinogenesis in rats was inhibited by low protein diets (Campbell, 2007, Madhavan and Gopalan, 1968). Using an experimental model of cancer, it was shown that the amount of protein fed after the initiation stage of cancer controlled the development of tumors independent of the amount of carcinogen (Youngman and Campbell, 1991). Growth was repressed by the low protein (5% of calories with casein as protein source) diet compared to the higher protein diet (20% calories as protein). If the higher animal protein diet was replaced with plant protein, a similar reduction occurred (Youngman and Campbell, 1992). The study also showed that the early lesions that led to tumors could be increased or decreased by changes in dietary protein intake at different times during the experiment (Youngman and Campbell, 1991). Even changing the diet after tumors had developed resulted in substantial reduction in tumor burden compared to those animals maintained on a higher protein diet. Similar responses to dietary protein were found using a viral initiator to produce liver cancer in mice (Cheng et al., 1997, Hu et al., 1997).

More recently a study, reported in 2013, confirms the association of dietary protein and cancer (Fontana et al., 2013). A 7% protein diet led to a 70% inhibition in tumor growth in prostate xenografts and 56% inhibition in breast xenografts in mice compared to an isocaloric diet of 21%

protein. Similar to results of Campbell et al., they also found using 20% plant protein inhibited tumor growth 37% compared to the same amount of animal protein.

Mechanisms suggested as mediating the effect of diet on cancer include signaling pathways involving mammalian target of rapamycin (mTOR) which is present in two cellular complexes, mTORC1 and mTORC2 (Guertin and Sabatini, 2007). mTOR responds to nutrients (glucose and amino acids), growth factors (such as insulin and insulin-like-growth factor (IGF1)), energy and stress (Melnik, 2012, Zoncu et al., 2011). Energy is sensed through the ratio of AMP to ATP. Glycolysis and mitochondrial respiration convert nutrients to ATP (high energy). With a drop in nutrients, ATP decreases as energy is used and not replenished producing AMP. The role of mTOR in integrating growth factor signals, nutrient and energy status is to promote cell growth and metabolism under favorable conditions (when activated) and to suppress protein synthesis and to promote recycling of cell proteins (autophagy) under low nutrient conditions (when inhibited). A key pathway leading to mTOR activation is through phosphatidylinositol-3-kinase (PI3k)/Akt (Porta et al., 2014). Through evolution mammals developed the ability to maximize use of nutrients to accommodate periods of abundance and periods of limited availability. During periods of fasting the drop in glucose and amino acids leads to a drop in insulin and an increase in the ratio of AMP to ATP indicative of low energy thus inhibiting activation of mTOR (Zoncu et al., 2011). Some amino acids appear to act more strongly on mTORC1 signaling than others (Yan and Lamb, 2012). It is likely that the differential effect of plant versus animal protein is at least partly due to their different amino acid profiles with different abilities to influence mTOR signaling. Dairy proteins and meat provide high amounts of leucine as well as stimulate insulin and IGF-1 (Melnik, 2012). Leucine robustly activates mTORC1 promoting protein synthesis, and its deprivation inhibits mTORC1 signaling suppressing protein synthesis (Yan and Lamb, 2012). Increased levels of IGF-1

are associated with increased risk of cancer, and protein intake is one of the most important dietary regulators of circulating IGF-1. Growth factors such as IGF-1 affect signaling pathways that activate mTOR (see Figures 2 and 3 in Zoncu et al. (2011) for a schematic of pathways involving mTOR). These systems evolved to promote survival under conditions in which nutrients were in short supply, which was a frequent occurrence during mammalian evolution. The constant availability and intake of food we experience today leads to chronic activation of mTOR and potentially to aberrant cell responses (Zoncu et al., 2011). The reduction in plasma insulin and IGF-1 levels in vegans consuming a moderate protein diet is thought to be an important factor in the reduced incidence and mortality of the "Western" cancers – breast, prostate, colon, pancreas, ovary in this group (McCarty, 2014).

Cholesterol

Cholesterol is a lipid important in the formation and stabilization of membranes. Transformed cells take up low density lipoproteins (LDL), the circulating source of cholesterol at higher rates than normal. LDL receptors are overexpressed in several cancer cell lines consistent with the increased synthesis of new membranes associated with proliferation. Abnormal cholesterol metabolism reflected by an increase in cholesteryl esters has been observed in tumor cell lines, experimental tumors and human tumors (Antalis and Buhman, 2012, Tosi and Tugnoli, 2005). ER- breast cells are reported to have a greater ability to take up and store exogenous cholesterol resulting in a proliferative advantage (Antalis et al., 2010). This is consistent with the slightly greater effect of dietary fat reduction in reducing breast cancer recurrence in ER- cancers.

Signals arising outside the tumor cell must cross the lipid membrane barrier to affect change. It is suggested that alterations in the lipid membrane structure due to cholesterol can influence signal

transduction mechanisms related to cancer (Freeman et al., 2007). Antalis and Buhman (2012) review epidemiology and mechanistic studies of the relationship among lipoproteins, cholesterol and cancer.

Fiber

The positive effect of fiber intake on CRC could be associated with rapid intestinal transit times leaving less time for carcinogens such as N-nitroso compounds to act upon the mucosa. Another possible mechanism to explain fiber's role in reducing CRC risk, is through the production of butyrate (Segal et al., 2000). The gut microbiota thrive on fermenting non-digestible fiber, and release butyrate as a metabolite. The cells of the colon are especially adept at using butyrate, a short chain fatty acid, as a form of energy, instead of glucose. It is estimated that the colonocytes get up to 70% of their energy from butyrate and other short chain fatty acids (Roediger, 1980). When relatively low amounts of butyrate are produced, it is rapidly metabolized by the mitochondria of the colonocytes, leading to increased proliferation. However, when there is an excess of butyrate, it accumulates in the nucleus, where it can act through an epigenetic mechanism as a histone deacetylase (HDAC) inhibitor. Histone modification by hyperacetylation results in transcriptionally active chromatin whereas deacetylation by histone deacetylase (HDAC) results in diminished accessibility for transcription. Thus the accumulation of butyrate results in reduced proliferation and increased apoptosis through HDAC inhibition (Bultman, 2014). In the case of cancer, colonocytes exhibit the increased glucose uptake and fermentation to lactate known as aerobic glycolysis or the Warburg effect. In this condition the mitochondria do not readily metabolize butyrate. Thus butyrate accumulates in the cell to low mM concentrations, resulting in cell cycle arrest and apoptosis through HDAC inhibition (Donohoe et al., 2012, Donohoe et al., 2014). Epigenetic modulation by HDAC inhibitors has long been suggested as a

potential cancer therapy. Indeed, more potent pharmacological HDAC inhibitors, such as Vorinostat, are currently approved for the treatment of cutaneous T-cell lymphoma and are being tested in a number of clinical trials for the treatment of other cancers (Mottamal et al., 2015). These pharmacological HDAC inhibitors act in the same manner as butyrate does naturally in the colon. While much of the work on dietary fiber has been done on model systems, it has also been shown that butyrate concentrations are elevated in human colorectal adenocarcinoma cells (Donohoe et al., 2014). Additionally, two epidemiological studies found that CRC patients had significantly less butyrate-producing bacteria than healthy controls (Balamurugan et al., 2008, Wang et al., 2012). The benefits of dietary fiber in reducing cancer risk may not be exclusively associated with reduced colorectal cancer risk. Two recent studies have also suggested an inverse relationship between dietary fiber and breast cancer risk (Bradbury et al., 2014, Liu et al., 2014).

Mechanisms (micronutrient intake)

The focus on the macronutrients protein, fat and their restriction however is only part of the story. Epidemiology studies have consistently shown that diets high in fruits and vegetables and whole grains are associated with decreased risk of diseases such as cancer and cardiovascular disease (CVD) (Willett, 1995, Willett, 2002). Phytochemicals are the bioactive compounds in food. These include phenolics, flavonoids, phenolic acids, carotenoids, etc. (Liu, 2004). They are protective against oxidative stress from free radicals and can be important in restricting the development and progression of cancer by inhibiting cell proliferation, inducing cell-cycle arrest and apoptosis and acting as antiangiogenesis factors.

Inositol hexaphosphate (phytic acid or IP6) is found in grains, nuts, seeds and legumes and is present in almost all mammalian cells. Known to be an antioxidant IP6 has been recognized in

cancer prevention and control of experimental tumors. As a cancer preventive agent, it was effective in experimental models given before or after carcinogen administration. It was shown to be effective in colon, breast, skin cancer and liver cancer models (Vucenik and Shamsuddin, 2006). IP6 normalizes proliferation and induces differentiation and maturation of malignant cells and has anti-angiogenic activity (Vucenik et al., 2004). IP6 can regulate the cell cycle to control cell division and force malignant cells to differentiate or go into apoptosis. The signaling processes underlying the effect of IP6 on cancer are under investigation (Fu et al., 2016, Liu et al., 2015). In the past IP6 has been considered an anti-nutrient due to its ability to chelate minerals such as iron, copper and zinc hindering absorption however recent studies show that this is only when very high IP6 is consumed in combination with a nutrient poor diet (Silva and Bracarense, 2016). There is currently much interest in its anticancer properties.

Lignans along with isoflavones are a class of phytoestrogens. Plant lignans are found in high concentrations in flaxseeds and sesame seeds but also in sprouts, fruits, berries, vegetables, whole grains and green tea (Buck et al., 2010). Lignans are metabolized in the gut into bioavailable metabolites. Proposed mechanisms of action in cancer include reduction of angiogenesis and stimulation of apoptosis (Bergman Jungestrom et al., 2007, Mense et al., 2008). Flaxseeds were able to inhibit proliferation of ER+ and ER- tumor cells and were associated with decreased IGF-1 and epidermal growth factor (Chen et al., 2004, Chen et al., 2002). It is also possible that other constituents accompanying lignans may have a protective effect (Buck et al., 2010). A meta-analysis on epidemiologic studies of the association of lignans and breast cancer risk found high plant lignan intake was associated with a risk reduction especially in postmenopausal women (Buck et al., 2010). In another study it was found that higher lignan intake may be associated with improved survival among postmenopausal women with breast cancer (McCann et al., 2010). In

general more favorable breast tumors biomarkers were associated with higher lignan intake (Ha et al., 2006). In a German case-control study, reduced breast cancer risk was associated with soybean, sunflower and pumpkin seeds in postmenopausal women, which did not depend upon ER status (Zaineddin et al., 2012). In breast cancer the action of phytoestrogens may be partially hormonal through a weak inhibitory effect on aromatase (the enzyme involved in the biosynthesis of estrogen) thus reducing levels of circulating estrogen (references in Zaineddin et al).

A review of the effect of dietary phytochemicals on angiogenesis in breast cancer was reported in 2012 (see Figure 1 in Reuben et al. (2012)). However, angiogenesis is a component of all tumor growth not just breast cancer. Dietary phytochemicals influence cellular physiology and homeostasis, and therefore likely the equilibrium between pro and antiangiogensis factors (Bhat and Singh, 2008). There are many potential targets in the angiogenesis process. Vascular endothelial growth factor (VEGF), a signaling protein that stimulates growth of new blood vessels, is the most important regulator of human tumor angiogenesis (Carmeliet, 2003). Other factors include fibroblast growth factors, tumor necrosis factor alpha, interleukin-8. The catechins in tea have been shown in cell lines to inhibit proliferation by suppressing factors associated with angiogenesis (Reuben et al., 2012). The phytochemical curcumin, in the spice turmeric, has been shown to have anticancer properties in a number of breast cancer cell lines through a variety of mechanisms related to angiogenesis (Carroll et al., 2008, Schindler and Mentlein, 2006, Shao et al., 2002). Also it has been shown effective in animal models of cancer (Anand et al., 2008). Ellagitannins, polyphenols in nuts and fruit such as almonds, walnuts, raspberries, strawberries and especially pomegranates have anticancer and antiangiogenic properties (Heber, 2008). Soy isoflavones (genistein the main soy isoflavone) have been shown to be cytotoxic against breast cancer cell lines (Banerjee et al., 2008) and has been shown to inhibit several angiogenic factors

(Valachovicova et al., 2004, Yu et al., 2004). Secretion of VEGF is inhibited by lignan metabolites (Bergman Jungestrom et al., 2007, Saarinen et al., 2008). Resveratrol, a phytochemical in grapes, has been widely studied and shown to be associated with a reduction in VEGF secretion in cells after treatment with the phytochemical (Garvin et al., 2006). Silymarin, a mixture of polyphenols (in artichokes, also in some spices and grapes, peanuts and berries), is also antiangiogenic (Jiang et al., 2000). Isothiocyanates, such as sulforaphane (in broccoli, cauliflower, cabbage and kale), exert a toxic effect on tumor cells (Jackson and Singletary, 2004, Johnston, 2004). Although the above examples involve cell lines, Reuben et al (2012) also cite in vivo evidence for the antiangiogenic properties of these dietary phytochemicals. Lycopene (in tomatoes) the most abundant source of the carotenoids and proanthocyanidins in grapes have antiangiogenic properties in *in vivo* rodent studies. The fact that the phytochemicals act in a variety of ways targeting different angiogenic factors when used collectively from a variety of foods in the diet implies that they will have greater preventive as well as therapeutic efficacy (Reuben et al., 2012).

Salicylates are widely distributed throughout the plant kingdom where they act as a defense mechanism against pathogens and environmental stress. Isothiocyanates are also part of plant defenses and are formed under conditions of physical injury. In mammalian cells salicylic acid (SA) acts to inhibit prostaglandins arising from COX-2 catalysis of arachidonic acid (Duthie and Wood, 2011). The acetylated form of SA is aspirin, which has therapeutic benefit in chronic inflammation and has been linked to decreased risk of several cancers (Baron, 2003, Vainio et al., 1997). The cyclooxygenases COX-1 and COX-2 are frequently overexpressed in many cancers. The prostaglandins produced from them can act on the lymphatic vasculature leading to increased metastasis (Karnezis et al., 2012). The anticancer effects of non-steroidal anti-inflammatory drugs are thought to be due to inhibitory effects on the COX enzymes. Salicylates are readily absorbed

from food and may contribute to the effects of fruit and vegetable consumption on lowering the risk of disease (Duthie and Wood, 2011). Urinary excretion of salicylates was found to be increased in vegetarians compared to non-vegetarians (Lawrence et al., 2003). Spices especially have high concentrations of salicylates and may be a contributing factor in the low cancer incidence in rural India (Paterson et al., 2006). SA levels in serum from rural Indians were found to be almost 3 fold higher than in Western vegetarians.

Phytosterols represent another class of compounds with anticancer properties. They are similar in structure and function to cholesterol but occur naturally in plants particularly nuts, seeds, cereals and legumes, and a review of their anticancer properties has recently been published (Shahzad et al., 2017). Epidemiology studies indicate lower risks of esophageal and ovarian cancers with dietary intake of beta-sitosterol and stigmasterol, two common phytosterols in the human diet (references in Shahzad et al). Modes of action have been investigated in cell lines and include increased apoptosis and cell cycle arrest.

The recurrence of cancer after treatment as well as treatment resistance has been linked to the existence of cancer stem cells which have the capacity for self-renewal (Kim and Surh, 2015). Dietary phytochemicals, genistein, sulforaphorane, curcumin and the tea catechin, epigallocatechin (EGCG), target multiple pathways involved in self-renewal, maintenance and growth of stem cells.

Dietary components can also affect the expression of genes associated with physiological processes through epigenetics. The primary mechanisms are DNA methylation, histone modifications and RNA silencing through micro RNAs (miRNA) (Supic et al., 2013). Two patterns of DNA methylation have been observed. Hypomethylation leads to activation of genes in tumor

progression, whereas hypermethylation leads to silencing of tumor suppressor genes. Histone modification also occurs through acetylation and deacetylation resulting in transcriptionally active or inactive chromatin, respectively. MiRNAs involved in posttranscriptional control of gene expression, regulate cell proliferation, differentiation and apoptosis. Bioactive food components can alter the expression of genes at the transcriptional level. This offers the potential of restoring to normal the aberrant disease associated epigenetic profile through a change in diet. Supic et al. (2013) discuss the relationship between nutrition and epigenetics and the effect upon cancer identifying compounds and classes of compounds that influence epigenetics through the three mechanisms described above. Many appear to work in all mechanisms. These include tea polyphenols (EGCG), soy isoflavones (genistein), resveratrol and curcumin. The B vitamin folate is active in DNA methylation and miRNA, and the isothiocyanate, sulforaphane and components in garlic act through histone modifications. A review of research relating nutritional epigenetics and hepatocellular carcinoma (HCC), noted that epigenetic changes were found in major processes related to the development of HCC (Moreno et al., 2016). The green tea component EGCG, active in the prevention of many cancers, has been shown to inhibit liver carcinogenesis and preneoplastic states in experimental animal models. EGCG also induced DNA demethylation and reactivated tumor suppressor genes that were hyper-methylated (Singh et al., 2011). Resveratrol in addition to other protective effects was found to inhibit HDACs in hepatocarcinogenesis (Bishayee et al., 2010). The isothiocyanate sulforaphane exhibits a strong inhibitory effect on HDACs and has been studied in several models of human cancer (Ho et al., 2009). A review of the regulatory effects of curcumin, a component of the spice turmeric, on epigenetics reports studies that document demethylation associated with reactivation of tumor suppressor genes (Teiten et al., 2013). Curcumin also modulates HDAC activity. The ketone body beta-hydroxybutyrate

produced in the fasting state as well as in the gut in response to fiber is an endogenous HDAC inhibitor (Shimazu et al., 2013). A recent review explores phytochemical effects on the epigenome (Zam and Khadour, 2017). Epigenetics and cancer is a rapidly expanding field.

In addition to specific phytochemicals, research has also focused on anticancer properties of the whole food. Berries for example have consistently shown anticancer properties both *in vivo* and *in vitro*. An investigation of the anticancer properties of berry juices in five cancer cell lines found that inhibition of proliferation involved cell cycle arrest (Boivin et al., 2007). Arrest of the G1 phase of the cell cycle was also found in a grape seed extract in prostate cancer cells (Agarwal et al., 2000). There were observed differences between berries in their preventive abilities against different cell lines indicating the importance of eating a wide variety. Notably antiproliferation was not linked to antioxidant properties. In a number of preclinical studies, berries have been shown to protect against oral and colon cancers (Bi et al., 2010, Casto et al., 2013, Harris et al., 2001). A freeze-dried strawberry powder was found to inhibit esophageal squamous cell carcinoma induced by N-nitrosomethylbenzylamine in the rat (Chen et al., 2006). Based on these results the effect of strawberry powder was investigated in a small prevention trial in China using subjects diagnosed with premalignant lesions (Chen et al., 2012). They demonstrated that the powder slowed the progression of the precancerous growth. The effect was at least partly due to decreased expression of inducible nitric oxide synthase (iNOS), COX-2, (two enzymes upregulated in esophageal cancer in the rat), and of Ki-67, a nuclear protein associated with cell proliferation, as well as inhibition of mTOR signaling (Chen et al., 2012, Chen et al., 2006).

Aromatase is an enzyme that converts androgens to estrogen and has been a target in the treatment of breast cancer for tumors, which are ER positive. The common white button

mushroom can significantly inhibit aromatase activity and could play a significant role in prevention of primary or recurrent breast cancer (Grube et al., 2001). Interestingly estrogen receptors are expressed in healthy and tumor lung tissue and estrogen can induce cell proliferation in vivo and in vitro (Shimazu et al., 2010).

The above discussion on the micronutrient content of food and its relation to cancer prevention is by no means a complete review but is meant to indicate the importance of known micronutrients (and others not yet discovered) in preventing disease.

Mechanisms (Food restriction)

Food restriction in general has been shown to be beneficial in the treatment of disease. Tumor metabolism has been a potential target since the discovery by Otto Warburg that many cancer cells exhibit increased glucose uptake and fermentation to lactate even in the presence of oxygen (aerobic glycolysis). It is now known that this occurs even with functioning mitochondria (Liberti and Locasale, 2016). The increased glucose uptake in cancer cells is the basis for the [^{18}F] labeled fluorodeoxyglucose (FDG) PET signal. Animal studies of fasting protocols have shown positive results in prevention as well as treatment in cancer. A number of studies in animal models have shown that a reduction in calorie intake without malnutrition reduces cancer incidence (Fontana and Klein, 2007, Hursting et al., 2003). The reduction in glucose levels as a result of fasting places stress on cancer cells, which rely on a ready supply of glucose. Fasting, calorie restriction (CR) and a carbohydrate limited ketogenic diet have been used to limit the availability of glucose and slow cancer progression in both animal and human studies (Hursting et al., 2003, Lee et al., 2012, Longo and Fontana, 2010, Mukherjee et al., 2002). These studies involved long term CR with weight loss, which would not be suitable for a patient group. However, it has been shown that short term

dietary restriction (fasting) can protect yeast, mammalian cells and mice from the toxic effects of chemotherapy (Raffaghello et al., 2008). While normal cells are protected by reallocating energy resources away from growth processes, cancer cells are not protected. This has been termed differential stress resistance (DSR). The mechanism for this is suggested to be the same as observed in protein restriction namely a reduction in free IGF-1 (Raffaghello et al., 2008, Safdie et al., 2009). While reduced IGF-1 shifts normal cells into a maintenance phase (via mTOR inactivation), cancer cells exhibit insensitivity to these anti-growth signals and continue dividing. Fasting has also been shown to differentially regulate many genes associated with cellular proliferation. The coupling of chemotherapy with prior short term fasting has recently been shown to increase sensitivity of cancer cells to chemotherapeutic drugs. In mouse models of neuroblastoma, fasting with chemotherapy resulted in long term survival without long term weight loss (Lee et al., 2012). In fact, cycles of fasting were shown to be as effective as chemotherapy in delaying progression of different tumors. These positive effects of fasting in cancer treatment and prevention are in contrast to the fact that obesity is linked to an increased incidence of cancer and worse outcomes in response to treatment (Khandekar et al., 2011).

Exploring the mechanisms of food restriction several studies have reported effects of fasting on the immune system (Cheng et al., 2014, DiBiase et al., 2016, Pietrocola et al., 2016). That fasting (at least 48 hours) lowers circulating IGF-1 levels and is able to protect mice from the toxicity of chemotherapy was shown by Lee et al (Lee et al., 2010). Building on this work, multiple cycles of fasting were found to lead to regeneration of hematopoietic stem cells thus reversing the immunosuppression caused by chemotherapy (Cheng et al., 2014). The mechanism was found to involve reduced PKA (cyclic adenosine monophosphate(cAMP) dependent protein kinase) signaling

in bone marrow cells due partly to the reduced IGF-1 levels. PKA, activated with the binding of cAMP, is a key regulator of processes related to cell growth and development. Regeneration of the immune system deficiency begins during the fasting period and completes with refeeding (Cheng et al., 2014).

More recently a low calorie, low protein fasting mimicking diet (FMD) developed by Brandhorst et al was used to test the effects of fasting and the FMD on the immune system in a mouse cancer model (Brandhorst et al., 2015, DiBiase et al., 2016). A trial in healthy human subjects of the FMD (plant based with reduced calorie (34 to 54% of normal) and protein (9-10%) intake) for 5 days a month for a cycle of 3 months) resulted in reduction of blood glucose by 11%, which remained lower after resuming a normal diet, a reduction in IGF-1 by 24% which remained lower (15%) after resuming the normal diet. In the mouse model, calories were restricted to 9.7% of the normal diet for 3 days while maintaining high nourishment (Brandhorst et al., 2015). This was found to be as effective as fasting for 2 days in reducing IGF-1. Three cycles of FMD increased circulating CD8+ lymphocytes.

Fasting is known to be one of the most efficient ways to elicit autophagy, degradation of cellular components (Mizushima et al., 2004). Fasting and a calorie restriction mimetic (CRM) were found to increase autophagy in tumor cells leading to an enhanced response to immunogenic chemotherapy in experimental tumor models (Pietrocola et al., 2016). Autophagy is required for the release of ATP into the extracellular space-attracting antigen presenting cells to the tumor. Short-term fasting or caloric restriction mimetics (CRM) that induce autophagy were found to improve inhibition of tumor growth by chemotherapy. The CRM used in this study to induce

autophagy was hydroxycitrate, an over the counter weight loss drug, which blocks production of acetyl CoA leading to extracellular accumulation of ATP (Pietrocola et al., 2016).

Fasting defined as water only or consuming very few calories (<200calorie/day) is distinct from calorie restriction, which is chronic reduction of calories maintaining meal frequency. Fasting can take different forms such as intermittent fasting for example fasting every other day or periodic fasting - 3 days every few weeks. However, recent studies have explored restricting food consumption to certain hours of the day, designated time restricted feeding. For example longer nightly fasting was associated with improvements in biomarkers of glycemic control and in a second study with lower C-reactive protein (Marinac et al., 2016, Marinac et al., 2015). A recent report suggests that time restricted feeding may be beneficial in preventing cancer recurrence (Marinac et al., 2016). A shorter nightly fasting duration (< 13 hrs) was associated with a 36% higher hazard for breast cancer recurrence. This suggests an alternative fasting protocol that may be easier to implement and more acceptable than fasting in the more traditional sense.

Supplements vs Whole Foods

The beta-carotene lung cancer studies present a cautionary tale in the use of supplements. Observational studies indicated lower lung cancer risk associated with carotenoid rich food particularly beta-carotene. Antioxidants such as beta-carotene protect cells from damage from reactive oxygen species (ROS). ROS and other free radicals may damage DNA leading to tumor formation. This idea led to trials using beta-carotene supplements. Examples include a double blind, placebo controlled trial on the prevention of lung cancer in older male cigarette smokers

supplementing with beta-carotene. The results showed no benefit and suggested an adverse outcome with more lung cancers diagnosed in the supplement group in (Albanes, 1999, Albanes et al., 1996). A second study also observed increased mortality in the supplemented group (Omenn et al., 1996). A more recent review of antioxidant supplements beta-carotene, vitamin A, vitamin C, vitamin E and selenium found no evidence to support supplements for primary or secondary prevention - and in fact beta-carotene and vitamin E seem to increase mortality (Bjelakovic et al., 2012). The effect of dietary antioxidants on a mouse model of lung cancer found increased proliferation within tumors (Sayin et al., 2014). This was found to be associated with reduced p53 (the product of a tumor suppressor gene) activation occurring in response to antioxidant-induced reduction in ROS and in DNA damage. This study was limited to effects on tumor progression not initiation or prevention. Other animal studies have shown that the potential toxic effects of dietary forms of beta-carotene are associated with high-risk behaviors of smoking and alcohol use (Forman et al., 2004). It seems that these types of studies should be done prior to human intervention trials. High folate intake through supplements may also be problematic. Although deficiency can increase risk of CRC in normal tissue supplementation can promote progression of existing cancer (Kim, 2007). However, a recent study found no association between naturally occurring folate or folic acid (from supplements) and cancer incidence in adults with ages greater than 57 years (Hu et al., 2016). A confounding factor in assessing folate and cancer is that wheat flour in the US has been fortified with folic acid since 1998. In the past few years, the focus has shifted to vitamin D, which has been linked to many diseases including autoimmunity, cancer, diabetes, cardiovascular disease (Welsh and Sattar, 2014). Vitamin D may be one exception to the previous negative findings of other supplements. A meta-analysis found a reduction in all-cause mortality with D3 supplementation but not D2 (Chowdhury et al., 2014). Recently Schwingshackl

et al. (2017) reported results from a meta-analysis of primary prevention trials of dietary supplements for cardiovascular disease and cancer. A decrease in cardiovascular mortality and disease was associated with vitamin E and folic acid supplements, while vitamin A was linked to an increased cancer risk and beta-carotene taken alone was associated with an increase in all-cause mortality. Both were taken in high doses. The conclusion was that while some supplements produced small beneficial effects, there was not sufficient evidence to support the use in primary prevention of cause-specific death. A supplement that may be of benefit is S-adenosylmethionine (SAMe), an endogenous universal methyl donor, which has been reported to block skeletal metastasis associated with prostate cancer in cell cultures and in mice inoculated with SAMe treated prostate cancer cells (Shukeir et al., 2015). Treatment of cells with SAMe led to a dose-dependent inhibition of proliferation, invasion and migration, and mice with SAMe treated cancer cells had fewer skeletal lesions. The action of SAMe in suppression of metastases is thought to be epigenetic through methylation of hypomethylated genes in pathways related to cell invasion and metastasis. This is in contrast to hypermethylation related to the inactivation of tumor suppressor genes. Shukeir et al. however found that the action of SAMe was selective leaving tumor suppressor genes unmethylated. They also suggest a possible preventive role in prostate cancer development. More studies are needed to confirm these results. SAMe has been available as an over the counter enteric coated supplement since 1999 used for depression, joint and liver support. It appears to be well tolerated and has been used in a number of studies of depression (Mischoulon et al., 2002, Papakostas et al.,2010). While there is evidence that some supplements may be of benefit, their use should be approached with caution particularly with respect to intake of excessive amounts of single nutrients.

It should be noted that vegan diets with no animal products require supplementation with B12. In any case, it seems unlikely that any one phytochemical will be found to be the magic bullet to prevent or arrest cancer. Also the concentrations of the phytochemicals that promote health are likely to be found in a range related to what can be obtained from plants in the diet, too little as well as too much can potentially cause harm. Furthermore the isolated compounds do not act in the same way as when present in the whole food. The combination of phytochemicals from variety of whole foods has a synergistic effect so that the combined activity is greater than any one "this explains why no single antioxidant can replace the combination of natural phytochemicals in fruits and vegetables" (Liu, 2004) .

Conclusion

A previous review and a recent meta-analysis conclude that vegetarian/vegan diets are a useful strategy for reducing risk of cancer (Lanou and Svenson, 2010, Dinu et al., 2016). In this review we have brought together data from epidemiology, clinical, and animal studies and data relating to the effects of macro and micro-nutrients, as well as studies on the effects of food restriction as in fasting and time restricted eating. In some cases the epidemiology and intervention studies presented confusing results due to the focus on fat without controlling for animal products. Also those studies done in Western countries generally did not have the range of fat or protein intake to see differences observed in countries with a lower consumption of animal products. We have also considered potential mechanisms by which diet can affect cancer risk or progression. The evidence points to a diet with minimal animal products. This reduces both animal protein and cholesterol and leaves room for a greater consumption of the micronutrients in fruits and vegetables. A common misperception is that adequate protein can only be obtained from animal

sources. Dietary analyses of more than 70,000 subjects from the Adventist Health Study 2 found that non-vegetarians consumed 75.8 g/d of total protein (58% from plants), while strict vegetarians (eating meat, fish, dairy or eggs not at all or less than once a month) consumed 72.3 g/d , (96% from plants)(Rizzo et al., 2013). Given that the recommended dietary allowance (RDA), which would be adequate for 97.5% of the population, is 45-56g/d, even the strict vegetarians are consuming more than enough protein. The most important aspect of diet with respect to cancer (and health in general) is the phytonutrient content that comes from the inclusion of a wide variety of fruits, vegetables, nuts, seeds, spices and tea. Diet in addition to some food restriction can potentially decrease the risk of cancer as well as increase the effectiveness of cancer treatment and decrease the risk of recurrence.

In addition to minimizing animal products, sugar, soda, pastries, desserts and processed foods in general (except for whole grain breads, pasta, rice etc.) should be minimized. Some foods that appear to be particularly beneficial with respect to cancer include: fruit, especially berries; a variety of vegetables (especially greens) raw and cooked, legumes (beans of any kind –black, pinto, lentils etc), nuts and seeds (especially flaxseeds, but also sunflower, sesame and pumpkin seeds), mushrooms, onions, garlic, spices (e.g. turmeric and other Indian spices), herbs and green tea. Many books and websites are available for recipes and menus for a vegan diet. Also some short-term fasting practiced periodically or just extended fasting between meals, for example between dinner and breakfast several times a week appears beneficial.

Experimental protocols to test the effect of diet on disease are much more difficult to design than those used to test drugs for which the “gold standard” is the double blind randomized controlled trial. These difficulties are discussed in a recent article in Nature about the use of diet to alleviate

symptoms of multiple sclerosis (Gupta, 2016). With dietary changes participants are not “blind” to which group they are in. Also it is very difficult to standardize diets in the way that drug doses are standardized. Nevertheless the evidence that has been accumulating for many years indicates that diet can affect disease in spite of the negative outcomes of some studies. It is therefore important that research strategies to study these effects be developed in spite of the difficulties. There are important clinical studies that do not fit into the classical research mode, but that does not mean they should not be done.

References

Agarwal C, Sharma Y ,Agarwal R. Anticarcinogenic effect of a polyphenolic fraction isolated from grape seeds in human prostate carcinoma DU145 cells: modulation of mitogenic signaling and cell-cycle regulators and induction of G1 arrest and apoptosis. *Mol Carcinog* 2000;**28:**129-38.

Albanes D. {beta}-Carotene and lung cancer: a case study. *Am J Clin Nutr* 1999;**69:**1345S-1350.

Albanes D, Heinonen OP, Taylor PR, Virtamo J, Edwards BK, Rautalahti M, et al. {alpha}-Tocopherol and beta-Carotene Supplements and Lung Cancer Incidence in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study: Effects of Base-line Characteristics and Study Compliance. *J Natl Cancer Inst* 1996;**88:**1560-1570.

Anand P, Sundaram C, Jhurani S, Kunnumakkara A ,Aggarwal B. Curcumin and cancer: an "old-age" disease with an "age-old" solution. *Cancer Lett* 2008;**267:**133-64.

Antalis CJ, Arnold T, Rasool T, Lee B, Buhman KK ,Siddiqui RA. High ACAT1 expression in estrogen receptor negative basal-like breast cancer cells is associated with LDL-induced proliferation. *Breast Cancer Res Treat* 2010;**122:**661-70.

Antalis CJ ,Buhman KK. 2012. *Lipoproteins and Cancer, Lipoproteins - Role in Health and Diseases,* [Online]. Available: http://www.intechopen.com/books/lipoproteins-role-in-health-and-diseases/lipoproteins-and-cancer.

Armstrong B ,Doll R. Environmental factors and cancer incidence and mortality in different countries, with special reference to dietary practices. *Int J Cancer* 1975;**15:**617-31.

Aune D, Chan DS, Lau R, Vieira R, Greenwood DC, Kampman E, et al. Dietary fibre, whole grains, and risk of colorectal cancer: systematic review and dose-response meta-analysis of prospective studies. *BMJ* 2011;**343:**d6617.

Balamurugan R, Rajendiran E, George S, Samuel GV ,Ramakrishna BS. Real-time polymerase chain reaction quantification of specific butyrate-producing bacteria, Desulfovibrio and Enterococcus faecalis in the feces of patients with colorectal cancer. *Journal of Gastroenterology and Hepatology (Australia)* 2008;**23:**1298-1303.

Banerjee S, Li Y, Wang Z ,Sarkar F. Multi-targeted therapy of cancer by genistein. *Cancer Lett* 2008;**269:**226-42.

Barnard R, Ngo T, Leung P, Aronson W ,Golding L. A low-fat diet and/or strenuous exercise alters the IGF axis in vivo and reduces prostate tumor cell growth in vitro. *Prostate* 2003;**56:**201-6.

Baron J. Epidemiology of non-steroidal anti-inflammatory drugs and cancer. *Prog Exp Tumor Res* 2003;**37:**1-24.

Bergman Jungestrom M, Thompson LU ,Dabrosin C. Flaxseed and Its Lignans Inhibit Estradiol-Induced Growth, Angiogenesis, and Secretion of Vascular Endothelial Growth Factor in Human Breast Cancer Xenografts In vivo. *Clin. Cancer Res.* 2007;**13:**1061-1067.

Bhat TA ,Singh RP. Tumor angiogenesis--a potential target in cancer chemoprevention. *Food Chem Toxicol* 2008;**46:**1334-45.

Bi X, Fang W, Wang L-H, Stoner GD ,Yang W. Black raspberries inhibit intestinal tumorigenesis in Apc 1638+/- and Muc2-/- mouse models of colorectal cancer. *Cancer Prevention Research* 2010;**3:**1443-1450.

Bishayee A, Politis T ,Darvesh AS. Resveratrol in the chemoprevention and treatment of hepatocellular carcinoma. *Cancer Treat Rev* 2010;**36:**43-53.

Bjelakovic G, Nikolova D, Gluud L, Simonetti R ,Gluud C. Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases. *Cochrane Database Syst Rev* 2012;**14:**CD007176.

Boivin D, Blanchette M, Barrette S, Moghrabi A ,Beliveau R. Inhibition of cancer cell proliferation and suppression of TNF-induced activation of NFkB by edible berry juices. *Anticancer Research* 2007;**27:**937-948.

Bradbury KE, Appleby PN ,Key TJ. Fruit , vegetable , and fiber intake in relation to cancer risk: findings from the European Prospective Investigation into Cancer and Nutrition (EPIC) 1 – 4. *The American Journal of Clinical Nutrition* 2014;**100:**1-4.

Brandhorst S, Choi I, Wei M, Cheng C-W, Sedrakyan S, Navarrete G, et al. A periodic diet that mimics fasting promotes multi-system regeneration, enhanced cognitive performance and healthspan. *Cell Metabolism* 2015;**22:**86-99.

Buck K, Zaineddin AK, Vrieling A, Linseisen J ,Chang-Claude J. Meta-analyses of lignans and enterolignans in relation to breast cancer risk. *Am J Clin Nutr* 2010;**92:**141-153.

Bultman SJ. Molecular pathways: Gene-environment interactions regulating dietary fiber induction of proliferation and apoptosis via butyrate for cancer prevention. *Clinical Cancer Research* 2014;**20:**799-803.

Burkitt DP. Epidemiology of cancer of the colon and rectum. *Cancer* 1971;**28:**3-13.

Campbell T ,Junshi C. Diet and chronic degenerative diseases: perspectives from China. *Am J Clin Nutr* 1994;**59:**1153S-61S.

Campbell T, Parpia B ,Chen J. Diet, lifestyle, and the etiology of coronary artery disease: the Cornell China study. *Am J Cardiol* 1998;**82:**18T-21T.

Campbell TC. Dietary protein, growth factors and cancer. *The American Journal of Clinical Nutrition* 2007;**85:**1667.

Campbell TC. Untold nutrition. *Nutr Cancer* 2014;**66:**1077-82.

Carmeliet P. Angiogenesis in health and disease. *Nat Med* 2003;**9:**653-60.

Carroll C, Ellersieck M ,Hyder S. Curcumin inhibits MPA-induced secretion of VEGF from T47-D human breast cancer cells. *Menopause* 2008;**15:**570-4.

Carroll K, Braden L, Bell J ,Kalamegham R. Fat and cancer. *Cancer* 1986;**58:**1818-25.

Carroll KK. Experimental Evidence of Dietary Factors and Hormone-dependent Cancers. *Cancer Res.* 1975;**35:**3374-3383.

Carter J, Saxe G, Newbold V, Peres C, Campeau R ,Bernal-Green L. Hypothesis: dietary management may improve survival from nutritionally linked cancers based on analysis of representative cases. *J Am Coll Nutr* 1993;**12:**209-26.

Casto B, Knobloch TJ, Galioto RL, Yu Z, Accurso BT ,Warner BM. Chemoprevention of oral cancer by lyphilized strawberries. *Anticancer Research* 2013;**33:**4757-4766.

Chen J, Hui E, Ip T ,Thompson LU. Dietary Flaxseed Enhances the Inhibitory Effect of Tamoxifen on the Growth of Estrogen-Dependent Human Breast Cancer (MCF-7) in Nude Mice. *Clin. Cancer Res.* 2004;**10:**7703-7711.

Chen J, Stavro P ,Thompson L. Dietary flaxseed inhibits human breast cancer growth and metastasis and downregulates expression of insulin-like growth factor and epidermal growth factor receptor. *Nutr Cancer* 2002;**43:**187-92.

Chen T, Hwang H, Rose ME, Nines RG ,Stoner GD. Chemopreventive Properties of Black Raspberries in N-Nitrosomethylbenzylamine-Induced Rat Esophageal Tumorigenesis:

Down-regulation of Cyclooxygenase-2, Inducible Nitric Oxide Synthase, and c-Jun. *Cancer Res.* 2006;**66:**2853-2859.

Chen T, Yan F, Qian J, Guo M, Zhang H, Tang X, et al. Randomized phase II trial of lyophilized strawberries in patients with dysplastic precancerous lesions of the esophagus *Cancer Prevention Research* 2012;**5:**41-50.

Cheng C-W, Adams G, Perin L, Wei M, Zhou X, Lam B, et al. Prolonged fasting reduces IGF-1/PKA toomote hematopoietic-stem-cell-based regeneration and reverse immunosuppresiion. *Cell Stem Cell* 2014;**14:**810-823.

Cheng Z, Hu J, King J, Jay G ,Campbell T. Inhibition of hepatocellular carcinoma development in hepatitis B virus transfected mice by low dietary casein. *Hepatology* 1997;**26:**1351-4.

Chlebowski RT. Nutrition and physical activity influence on breast cancer incidence and outcome. *Breast* 2013;**22 Suppl 2:**S30-7.

Chlebowski RT, Blackburn GL, Thomson CA, Nixon DW, Shapiro A, Hoy MK, et al. Dietary fat reduction and breast cancer outcome: interim efficacy results from the Women's Intervention Nutrition Study. *J Natl Cancer Inst* 2006;**98:**1767-76.

Chowdhury R, Kunutsor S, Vitezova A, Oliver-Williams C, Chowdhury S, Kiefte-De-Jong JC, et al. Vitamin D and risk of cause specific death: systematic review and meta-analysis of observational cohort and randomised intervention studies. *BMJ* 2014;**348:**g1903-.

Danilo C ,Frank PG. Cholesterol and breast cancer development. *Curr Opin Pharmacol* 2012;**12:**677-82.

Dibiase S, Lee C, Brandhorst S, Manes B, Buono R, Cheng C-W, et al. Fasting-mimicking diet reduces HO-1 to promote T cell-mediated tumor cytotoxicity. *Cancer Cell* 2016;**30:**136-146.

Dinu M, Abbate R, Gensini GF, Casini A ,Sofi F. Vegetarian, vegan diets and multiple health outcomes: a systematic review with meta-analysis of observational studies. *Crit Rev Food Sci Nutr* 2016**:**0.

Donohoe DR, Collins LB, Wali A, Bigler R, Sun W ,Bultman SJ. The Warburg Effect Dictates the Mechanism of Butyrate-Mediated Histone Acetylation and Cell Proliferation. *Molecular Cell* 2012;**48:**612-626.

Donohoe DR, Holley D, Collins LB, Montgomery SA, Whitmore AC, Hillhouse A, et al. A gnotobiotic mouse model demonstrates that dietary fiber protects against colorectal tumorigenesis in a microbiota- and butyrate-dependent manner. *Cancer Discovery* 2014;**4:**1387-1397.

Duthie G ,Wood A. Natural salicylates: foods, functions and disease prevention. *Food Funct* 2011;**2:**515-20.

Esselstyn C. Updating a 12-year experience with arrest and reversal therapy for coronary heart disease (an overdue requiem for palliative cardiology). *Am J Cardiol* 1999;**84:**339-41, A8.

Fontana L, Adelaiye RM, Rastelli AL, Miles KM, Ciamporcero E, Longo VD, et al. Dietary protein restriction inhibits tumor growth in human xenograft models of prostate and breast cancer. *Oncotarget* 2013;**4:**2451-2461.

Fontana L ,Klein S. Aging, adiposity, and calorie restriction. *JAMA* 2007;**297:**986-94.

Fontana L, Klein S ,Holloszy JO. Long-term low-protein, low-calorie diet and endurance exercise modulate metabolic factors associated with cancer risk. *Am J Clin Nutr* 2006;**84:**1456-1462.

Forman MR, Hursting SD, Umar A ,Barrett JC. Nutrition and cancer prevention: a multidisciplinary perspective on human trials. *Annu Rev Nutr* 2004;**24:**223-54.

Frattaroli J, Weidner G, Dnistrian A, Kemp C, Daubenmier J, Marlin R, et al. Clinical events in prostate cancer lifestyle trial: results from two years of follow-up. *Urology* 2008;**72:**1319-23.

Freeman MR, Cinar B, Kim J, Mukhopadhyay NK, Di Vizio D, Adam RM, et al. Transit of hormonal and EGF receptor-dependent signals through cholesterol-rich membranes. *Steroids* 2007;**72:**210-7.

Fu M, Song Y, Wen Z, Lu X ,Cui L. Inositol Hexaphosphate and Inositol Inhibit Colorectal Cancer Metastasis to the Liver in BALB/c Mice. *Nutrients* 2016;**8**.

Garvin S, Ollinger K ,Dabrosin C. Resveratrol induces apoptosis and inhibits angiogenesis in human breast cancer xenografts in vivo. *Cancer Lett* 2006;**231:**113-22.

Grube BJ, Eng ET, Kao Y-C, Kwon A ,Chen S. White Button Mushroom Phytochemicals Inhibit Aromatase Activity and Breast Cancer Cell Proliferation. *J. Nutr.* 2001;**131:**3288-3293.

Guertin DA ,Sabatini DM. Defining the role of mTOR in cancer. *Cancer cell* 2007;**12:**9-22.

Gupta S. Diet: Changing the recipe. *Nature* 2016;**540:**S13-S14.

Ha T, Lyons-Wall P, Moore D, Tattam B, Boyages J, Ung O, et al. Phytoestrogens and indicators of breast cancer prognosis. *Nutr Cancer* 2006;**56:**3-10.

Harris G, Gupta A, Nines R, Kresty L, Habib S, Frankel W, et al. Effects of lyophilized black raspberries on azoxymethane-induced colon cancer and 8-hydroxy-2'-deoxyguanosine levels in the Fischer 344 rat. *Nutr Cancer* 2001;**40:**125-33.

Heber D. Multitargeted therapy of cancer by ellagitannins. *Cancer Lett* 2008;**269:**262-8.

Ho E, Clarke JD ,Dashwood RH. Dietary Sulforaphane, a Histone Deacetylase Inhibitor for Cancer Prevention. *J. Nutr.* 2009;**139:**2393-2396.

Hu F, Stampfer M, Manson J, Rimm E, Colditz G, Rosner B, et al. Dietary fat intake and the risk of coronary heart disease in women. *N Engl J Med* 1997;**337:**1491-9.

Hu J, Juan W ,Sahyoun NR. Intake and Biomarkers of Folate and Risk of Cancer Morbidity in Older Adults, NHANES 1999-2002 with Medicare Linkage. *PloS one* 2016;**11:**e0148697.

Hu J, La Vecchia C, De Groh M, Negri E, Morrison H ,Mery L. Dietary cholesterol intake and cancer. *Ann Oncol* 2012;**23:**491-500.

Hursting S, Lavigne J, Berrigan D, Perkins S ,Barrett J. Calorie restriction, aging, and cancer prevention: mechanisms of action and applicability to humans. *Annu Rev Med* 2003;**54:**131-52.

Jackson SJT ,Singletary KW. Sulforaphane inhibits human MCF-17 mammary cancer cell mitotic progression and tubulin polymerization. *The Journal of Nutrition* 2004;**134:**2229-2236.

Jiang C, Agarwal R ,Lu J. Anti-angiogenic potential of a cancer chemopreventive flavonoid antioxidant, silymarin: inhibition of key attributes of vascular endothelial cells and angiogenic cytokine secretion by cancer epithelial cells. *Biochem Biophys Res Commun* 2000;**276:**371-8.

Johnston N. Sulforaphane halts breast cancer cell growth. *Drug Discovery Today* 2004;**9**.

Karnezis T, Shayan R, Fox S, Achen MG ,Stacker SA. The connection between lymphangiogenic signalling and prostaglandin biology: A missing link in the metastatic pathway. *Oncotarget* 2012;**3:**890-903.

Key T, Appleby P, Spencer E, Travis R, Allen N, Thorogood M, et al. Cancer incidence in British vegetarians. *Br J Cancer* 2009;**101:**192-7.

Khandekar M, Cohen P ,Spiegelman B. Molecular mechanisms of cancer development in obesity. *Nat Rev Cancer* 2011;**11:**886-95.

Kim D-H ,Surh Y-J. Chemporeventive and therapeutic potential of phytocheemicals targeting cancer stem cells. *Current Pharmacology Reports* 2015;**1:**302-311.

Kim YI. Folate and colorectal cancer: An evidence-based critical review. *Molecular nutrition & food research* 2007;**51:**267-292.

Kitahara CM, Berrington De Gonzalez A, Freedman ND, Huxley R, Mok Y, Jee SH, et al. Total cholesterol and cancer risk in a large prospective study in Korea. *J Clin Oncol* 2011;**29:**1592-8.

Kolonel L, Hinds M ,Hankin J 1980. Cancer patterns among migrant and native born Japanese in Hawaii in relation to smoking, drinking and dietary habits. *In:* GELBOIN, H., MACMAHON, B., MATSUSHIMA, T., SUGIMURA, T., TAKAYAMA, S. & TAKEBE, H. (eds.) *Genetic and Environmental Factors in Experimental and Human Cancer*

Tokyo: Japan Scientific Socideties Press.

Kolonel L ,Wilkins L 2006. Migrant Studies. *In:* SCHOTTENFELD, D. & FRAUMENI, J. J. (eds.) *Cancer Epidemiology and Prevention, 3rd edn* NY: Oxford University Press, Inc.

Lanou A ,Svenson B. Reduced cancer risk in vegetarians: an analysis of recent reports. *Cancer Management and Research* 2010;**3:**1-8.

Lawrence JR, Peter R, Baxter GJ, Robson J, Graham AB ,Paterson JR. Urinary excretion of salicyluric and salicylic acids by non-vegetarians, vegetarians, and patients taking low dose aspirin. *J. Clin. Pathol.* 2003;**56:**651-653.

Lee C, Raffaghello L, Brandhorst S, Safdie FM, Bianchi G, Martin-Montalvo A, et al. Fasting Cycles Retard Growth of Tumors and Sensitize a Range of Cancer Cell Types to Chemotherapy. *Science Translational Medicine* 2012;**4:**124ra27-.

Lee C, Safdie FM, Raffaghello L, Wei M, Madia F, Parrella E, et al. Reduced Levels of IGF-I Mediate Differential Protection of Normal and Cancer Cells in Response to Fasting and Improve Chemotherapeutic Index. *Cancer Res.* 2010;**70:**1564-1572.

Liberti MV ,Locasale JW. The Warburg Effect: How Does it Benefit Cancer Cells? *Trends Biochem Sci* 2016;**41:**211-8.

Liu B, Mao Q, Wang X, Zhou F, Luo J, Wang C, et al. Cruciferous vegetables consumption and risk of renal cell carcinoma: a meta-analysis. *Nutr Cancer* 2013;**65:**668-76.

Liu G, Song Y, Cui L, Wen Z ,Lu X. Inositol hexaphosphate suppresses growth and induces apoptosis in HT-29 colorectal cancer cells in culture: PI3k/Akt pathway as a potential target. *Int J Clin Exp Path* 2015;**8:**1402-1410.

Liu RH. Potential Synergy of Phytochemicals in Cancer Prevention: Mechanism of Action. *J. Nutr.* 2004;**134:**3479S-3485.

Liu Y, Colditz GA, Cotterchio M, Boucher BA ,Kreiger N. Adolescent dietary fiber, vegetable fat, vegetable protein, and nut intakes and breast cancer risk. *Breast Cancer Research and Treatment* 2014;**145:**461-470.

Llaverias G, Danilo C, Mercier I, Daumer K, Capozza F, Williams TM, et al. Role of cholesterol in the development and progression of breast cancer. *Am J Pathol* 2011;**178:**402-12.

Longo V ,Fontana L. Calorie restriction and cancer prevention: metabolic and molecular mechanisms. *Trends Pharmacol Sci* 2010;**31:**89-98.

Louis P, Hold GL ,Flint HJ. The gut microbiota, bacterial metabolites and colorectal cancer. *Nat Rev Microbiol* 2014;**12:**661-72.

Madhavan T ,Gopalan C. The effect of dietary protein on carcinogenesis of aflatoxin. *Arch Pathol* 1968;**85:**133-7.

Marinac CR, Sandahl H, Nelson M, Breen CI, Hartman SJ, Natarajan L, et al. Prolonged nightly fasting and breast cancer prognosis. *JAMA Oncology* 2016;**2:**1049-1055.

Marinac CR, Sears DD, Natarajan L, Gallo LC, Breen CI ,Patterson RE. Frequency and Circadian Timing of Eating May Influence Biomarkers of Inflammation and Insulin Resistance Associated with Breast Cancer Risk. *PLoS One* 2015;**10**.

Mccann S, Thompson L, Nie J, Dorn J, Trevisan M, Shields P, et al. Dietary lignan intakes in relation to survival among women with breast cancer: the Western New York Exposures and Breast Cancer (WEB) Study. *Breast Cancer Res Treat* 2010;**122:**229-35.

Mccarty M. GCN2 and FGF21 are likely mediators of the protection from cancer, autoimmunity, obesity, and diabetes afforded by vegan diets. *Medical Hypotheses* 2014;**83:**365-371.

Melnik B. Leucine signaling in the pathogenesis of type 2 diabetes and obesity. *World Journal of Diabetes* 2012;**3:**38-53.

Mense S, Hei T, Ganju R ,Bhat H. Phytoestrogens and breast cancer prevention: possible mechanisms of action. *Environ Health Perspect* 2008;**116:**426-33.

Mizushima N, Yamamoto A, Matsui M, Yoshimori T ,Ohsumi Y. In Vivo Analysis of Autophagy in Response to Nutrient Starvation Using Transgenic Mice Expressing a Fluorescent Autophagosome Marker. *Mol. Biol. Cell* 2004;**15:**1101-1111.

Moreno F, Heidor R ,Pogribny I. Nutritional epigenetics and the prevention of hepatocellular carcinoma with bioactive food constituents. *Nutrition and Cancer* 2016;**68:**719-733.

Mottamal M, Zheng S, Huang TL ,Wang G. Histone deacetylase inhibitors in clinical studies as templates for new anticancer agents. *Molecules* 2015;**20:**3898-3941.

Mukherjee P, El-Abbadi M, Kasperzyk J, Ranes M ,Seyfried T. Dietary restriction reduces angiogenesis and growth in an orthotopic mouse brain tumour model. *Br J Cancer* 2002;**86:**1615-21.

Ngo T, Barnard R, Tymchuk C, Cohen P ,Aronson W. Effect of diet and exercise on serum insulin, IGF-I, and IGFBP-1 levels and growth of LNCaP cells in vitro (United States). *Cancer Causes Control* 2002;**13:**929-35.

O'keefe SJD, Chung D, Mahmoud N, Sepulveda AR, Manafe M, Arch J, et al. Why Do African Americans Get More Colon Cancer than Native Africans? *J. Nutr.* 2007;**137:**175S-182.

Omenn G, Goodman G, Thornquist M, Balmes J, Cullen M, Glass A, et al. Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease. *N Engl J Med* 1996;**334:**1150-5.

Ornish D, Brown S, Scherwitz L, Billings J, Armstrong W, Ports T, et al. Can lifestyle changes reverse coronary heart disease? The Lifestyle Heart Trial. *Lancet* 1990;**336:**129-33.

Ornish D, Weidner G, Fair W, Marlin R, Pettengill E, Raisin C, et al. Intensive lifestyle changes may affect the progression of prostate cancer. *J Urol* 2005;**174:**1065-9; discussion 1069-70.

Paterson J, Srivastava R, Baxter G, Graham A ,Lawrence J. Salicylic acid content of spices and its implications. *J Agric Food Chem* 2006;**54:**2891-6.

Patterson RE, Kristal A, Rodabough R, Caan B, Lillington L, Mossavar-Rahmani Y, et al. Changes in food sources of dietary fat in response to an intensive low-fat dietary intervention: early results from the Women's Health Initiative. *J Am Diet Assoc* 2003;**103:**454-60.

Pierce JP, Natarajan L, Caan BJ, Parker BA, Greenberg ER, Flatt SW, et al. Influence of a diet very high in vegetables, fruit, and fiber and low in fat on prognosis following treatment for

breast cancer: the Women's Healthy Eating and Living (WHEL) randomized trial. *JAMA* 2007;**298:**289-98.

Pietrocola F, Pol J, Vacchelli E, Rao S, Enot D, Baracco E, et al. Caloric restriction mimetics enhance anticancer immunosurveillance. *Cancer Cell* 2016;**30:**147-160.

Pollak MN, Schernhammer ES ,Hankinson SE. Insulin-like growth factors and neoplasia. *Nat Rev Cancer* 2004;**4:**505-18.

Popkin BM ,Du S. Dynamics of the Nutrition Transition toward the Animal Foods Sector in China and its Implications: A Worried Perspective. *J. Nutr.* 2003;**133:**3898S-3906.

Porta C, Paglino C ,Mosca A. Targeting PI3K/Akt/mTOR signaling in cancer. *Targeting PI3K/mTOR signaling in cancer* 2014**:**47.

Potter JD, Slattery ML, Bostick RM ,Gapstur SM. Colon cancer: a review of the epidemiology. *Epidemiol Rev* 1993;**15:**499-545.

Prentice RL, Caan B, Chlebowski RT, Patterson R, Kuller LH, Ockene JK, et al. Low-fat dietary pattern and risk of invasive breast cancer: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. *JAMA* 2006;**295:**629-42.

Raffaghello L, Lee C, Safdie FM, Wei M, Madia F, Bianchi G, et al. Starvation-dependent differential stress resistance protects normal but not cancer cells against high-dose chemotherapy. *PNAS* 2008;**105:**8215-8220.

Reuben S, Gopalan A, Petit D ,Bishayee A. Modulation of angiogenesis by dietary phytoconstituents in the prevention and intervention of breast cancer. *Mol Nutr Food Res* 2012;**56:**14-29.

Rizzo N, Jaceldo-Siegl K, Sabate J ,Fraser G. Nutrient profiles of vegetarian and nonvegetarian dietary patterns. *Journal of the Academy of nutrition and Dietetics* 2013;**113:**1610-1619.

Roediger WE. Role of anaerobic bacteria in the metabolic welfare of the colonic mucosa in man. *Gut* 1980;**21:**793-798.

Saarinen N, Warri A, Dings R, Airio M, Smeds A ,Makela S. Dietary lariciresinol attenuates mammary tumor growth and reduces blood vessel density in human MCF-7 breast cancer xenografts and carcinogen-induced mammary tumors in rats. *Int J Cancer* 2008;**123:**1196-204.

Safdie FM, Dorff T, Quinn D, Fontana L, Wei M, Lee C, et al. Fasting and Cancer Treatment in Humans: A Case series report

Aging (Albany NY) 2009;**1:**988-1007.

Sayin VI, Ibrahim MX, Larsson E, Nilsson JA, Lindahl P ,Bergo MO. Antioxidants accelerate lung cancer progression in mice. *Sci Transl Med* 2014;**6:**221ra15.

Schindler R ,Mentlein R. Flavonoids and Vitamin E Reduce the Release of the Angiogenic Peptide Vascular Endothelial Growth Factor from Human Tumor Cells. *J. Nutr.* 2006;**136:**1477-1482.

Schwingshackl L, Boeing H, Stelmach-Mardas M, Gottschald M, Dietrich S, Hoffmann G, et al. Dietary Supplements and Risk of Cause-Specific Death, Cardiovascular Disease, and Cancer: A Systematic Review and Meta-Analysis of Primary Prevention Trials. *Advances in Nutrition: An International Review Journal* 2017;**8:**27-39.

Segal I, Edwards CA ,Walker AR. Continuing low colon cancer incidence in African populations. *Am J Gastroenterol* 2000;**95:**859-60.

Shahzad N, Khan W, Md S, Ali A, Saluja SS, Sharma S, et al. Phytosterols as a natural anticancer agent: Current status and future perspective. *Biomed Pharmacother* 2017;**88:**786-794.

Shao Z, Shen Z, Liu C, Sartippour M, Go V, Heber D, et al. Curcumin exerts multiple suppressive effects on human breast carcinoma cells. *Int J Cancer* 2002;**98:**234-40.

Shimazu T, Hirschey MD, Newman J, He W, Shirakawa K, Le Moan N, et al. Suppression of Oxidative Stress by {beta}-Hydroxybutyrate, an Endogenous Histone Deacetylase Inhibitor. *Science* 2013;**339:**211-214.

Shimazu T, Inoue M, Sasazuki S, Iwasaki M, Sawada N, Yamaji T, et al. Isoflavone intake and risk of lung cancer: a prospective cohort study in Japan. *Am J Clin Nutr* 2010;**91:**722-728.

Silva EO ,Bracarense APFRL. Phytic Acid: from antinutritional to multiple protection factor in organic systems. *Journal of Food Science* 2016;**81:**R1357-R1362.

Silvester KR, Bingham SA, Pollock JR, Cummings JH ,O'neill IK. Effect of meat and resistant starch on fecal excretion of apparent N-nitroso compounds and ammonia from the human large bowel. *Nutr Cancer* 1997;**29:**13-23.

Singh B, Shankar S ,Srivastava R. Green tea catechin, epigallocatechin-3-gallate (): mechanisms, perspectives and clinical applications. *Biochem Pharmacol* 2011;**82:**1807-21.

Supic G, Jagodic M ,Magic Z. Epigenetics: A new link between nutrition and cancer. *Nutrition and Cancer* 2013;**65:**781-792.

Teiten M-H, Dicato M ,Diedrich M. Curcumin as a regulator of epigenetics events. *Molecular Nutrition and Food Research* 2013;**57:**1619-1629.

Thiébaut AC, Jiao L, Silverman DT, Cross AJ, Thompson FE, Subar AF, et al. Dietary fatty acids and pancreatic cancer in the NIH-AARP diet and health study. *Journal of the National Cancer Institute* 2009.

Tosi MR ,Tugnoli V. Cholesteryl esters in malignancy. *Clin Chim Acta* 2005;**359:**27-45.

Tymchuk C, Barnard R, Heber D ,Aronson W. Evidence of an inhibitory effect of diet and exercise on prostate cancer cell growth. *J Urol* 2001;**166:**1185-9.

Vainio H, Morgan G ,Kleihues P. An international evaluation of the cancer-preventive potential of nonsteroidal anti-inflammatory drugs. *Cancer Epidemiolgy, Biomarkers and Prevention* 1997;**6:**749-753.

Valachovicova T, Slivova V, Bergman H, Shuherk J ,Sliva D. Soy isoflavones suppress invasiveness of breast cancer cells by the inhibition of NF-kappaB/AP-1-dependent and -independent pathways. *Int J Oncol* 2004;**25:**1389-95.

Vucenik I, Passaniti A, Vitolo MI, Tantivejkul K, Eggleton P ,Shamsuddin AM. Anti-angiogenic activity of inositol hexaphosphate (IP6). *Carcinogenesis* 2004;**25:**2115-2123.

Vucenik I ,Shamsuddin A. Protection against cancer by dietary IP6 and inositol. *Nutr Cancer* 2006;**55:**109-25.

Wang T, Cai G, Qiu Y, Fei N, Zhang M, Pang X, et al. Structural segregation of gut microbiota between colorectal cancer patients and healthy volunteers. *The ISME Journal* 2012;**6:**320-329.

Welsh P ,Sattar N. Vitamin D and chronic disease prevention. *BMJ* 2014;**348:**g2280-.

Willett W. Diet, nutrition, and avoidable cancer. *Environ Health Perspect* 1995;**103 Suppl 8:**165-70.

Willett W, Hunter D, Stampfer M, Colditz G, Manson J, Spiegelman D, et al. Dietary fat and fiber in relation to risk of breast cancer. An 8-year follow-up. *JAMA* 1992;**268:**2037-44.

Willett WC. Balancing Life-Style and Genomics Research for Disease Prevention. *Science* 2002;**296:**695-698.

Wu S, Powers S, Zhu W ,A HY. Substantial contribution of extrinsic risk factors to cancer development. *Nature* 2016;**529:**43-47.

Yan L ,Lamb R. Amino acid sensing and regulation of mTORC1. *Semin Cell Dev Biol* 2012;**23:**621-5.

Youngman L ,Campbell T. The sustained development of preneoplastic lesions depends on high protein intake. *Nutr Cancer* 1992;**18:**131-42.

Youngman LD ,Campbell TC. High Protein Intake Promotes the Growth of Hepatic Preneoplastic Foci in Fischer #344 Rats: Evidence that Early Remodeled Foci Retain the Potential for Future Growth. *J. Nutr.* 1991;**121:**1454-1461.

Yu X, Mi M ,Zhu J. [Effect of genistein on expression of angiogenesis related factors in HER-2/neu-overexpressing breast cancer cells]. *Shi Yan Sheng Wu Xue Bao* 2004;**37:**251-3.

Zaineddin AK, Buck K, Vrieling A, Heinz J, Flesch-Janys D, Linseisen J, et al. The association between dietary lignans, phytoestrogen-rich foods, and fiber intake and postmenopausal breast cancer risk: a German case-control study. *Nutr Cancer* 2012;**64:**652-65.

Zam W ,Khadour A. Impact of Phytochemicals and Dietary Patterns on Epigenome and cancer. *Nutrition and Cancer* 2017;**69:**184-200.

Zhang J, Dhakal I, Zhao Z ,Li L. Trends in mortality from cancers of the breast, colon, prostate, esophagus, and stomach in East Asia: role of nutrition transition. *Eur J Cancer Prev* 2012;**21:**480-9.

Zoncu R, Efeyan A ,Sabatini DM. mTOR: from growth signal integration to cancer, diabetes and ageing. *Nature reviews Molecular cell biology* 2011;**12:**21-35.