Vegetables, fruits and phytoestrogens in the prevention of diseases

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ABSTRACT

The intake of 400–600 g/d of fruits and vegetables is associated with reduced incidence of many common forms of cancer, and diets rich in plant foods are also associated with a reduced risk of heart disease and many chronic diseases of ageing. These foods contain phytochemicals that have anti-cancer and anti-inflammatory properties which confer many health benefits. Many phytochemicals are colourful, and recommending a wide array of colourful fruits and vegetables is an easy way to communicate increased diversity of intake to the consumer. For example, red foods contain lycopene, the pigment in tomatoes, which is localized in the prostate gland and may be involved in maintaining prostate health, and which has also been linked with a decreased risk of cardiovascular disease. Green foods, including broccoli, Brussels sprouts and kale, contain glucosinolates which have also been associated with a decreased risk of cancer. Garlic and other white-green foods in the onion family contain allyl sulphides which may inhibit cancer cell growth. Other bioactive substances in green tea and soybeans have health benefits as well. Consumers are advised to ingest one serving of each of the seven colour groups daily, putting this recommendation within the United States National Cancer Institute and American Institute for Cancer Research guidelines of five to nine servings per day. Grouping plant foods by colour provides simplification, but it is also important as a method to help consumers make wise food choices and promote health.

KEY WORDS: Dietary patterns, cancer prevention, phytochemicals

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Human food choices and dietary patterns have been driven by necessity and economics and have been influenced by the promotion of foods more on their merits of taste, cost or convenience, and less for their nutritional merits or health value. The diversity of human dietary patterns around the world has been well documented, nevertheless patterns associated with a lower risk of chronic diseases including common forms of cancer have also be noted.[1] In examining these diverse patterns, a consistently higher intake of fruits, vegetables, whole grains and plant proteins such as soy – in comparison with the typical American diet – is associated with a markedly reduced risk of cancer, heart disease and some chronic diseases of ageing. In the nutrition science and epidemiological literature these dietary patterns have often been more simply characterised as low-fat, high-fibre diets. Such simplified terminologies led to the concept that fibre or phytochemical supplementation could reproduce the benefits of the healthy dietary patterns they represented, and ignored the benefits of not only the multitude of nutrients in plant foods, but also the health benefits of the dietary modality as a whole.

As a result of the concept that a dietary pattern conferred its benefits through a single component, trials have been conducted that purported to test one component of the diet in a given population while all the other variables were held constant. However, isolated pure compounds may lose their bioactivity, or may not behave in the same manner as they do when consumed from whole foods. The expected benefits were not realized for fibre supplementation[3] or b-carotene supplementation.[4] However, international studies suggest that for some cancers of the aerodigestive tract, dietary intakes of 400-600 grams of fruits and vegetables per day is associated with a 50% reduction in risk.[1]

Not only does a diet rich in plant foods provide essential vitamins and minerals, but also over 25,000 phytochemicals which cannot be provided by a typical Western pattern based on refined grains, added oils, sugar and salt. Traditional plant-based diets in other countries may be rich in many of these phytochemicals.[5] Recent studies of existing hunter-gatherer populations have revealed that these individuals eat more than 800 different varieties of plant-based foods,[6] but when they move into urban areas and begin eating so-called street foods, they begin to develop nutritional deficiencies.[7]

In the United States, most people eat only two to three servings of fruits and vegetables per day and a minority eat none at all.[8] The regular consumption of fruits and vegetables is associated with a reduced risk of cancer, cardiovascular disease, stroke and many functional declines associated with ageing,[9-11] and it has been estimated that one-third of all cancer deaths in the United States could be avoided through dietary modification which includes an abundant intake of fruits and vegetables.[12] Further, plant-based diets have a lower calorie

density and increased nutrient density which are important factors in curbing the obesity epidemic.

Phytochemicals in the Prevention of Cardiovascular Disease

Several studies have suggested a strong link between dietary phytochemical intake and a reduced risk for cardiovascular disease. Dietary flavonoids have been inversely correlated with mortality from coronary artery disease, plasma total cholesterol and low-density lipoprotein (LDL). Oxidized LDL has been proposed as an atherogenic factor in heart disease, promoting cholesterol ester accumulation and foam cell formation.[13,14] Dietary antioxidants from fruits and vegetables get incorporated into LDL, and become oxidized themselves, thus preventing oxidation of polyunsaturated fatty acids. Phytochemicals also reduce platelet aggregation, modulate cholesterol synthesis and absorption and reduce blood pressure.[15] Systemic inflammation may also be a critical factor in cardiovascular disease. C-reactive protein, an inflammatory marker, may be a stronger predictor of cardiovascular disease that LDL cholesterol,[16] and the anti-inflammatory activity of phytochemicals may play an important role in the health of the heart.

Anti-inflammatory Effects of Phytochemicals

Cytokines are peptide hormones secreted by inflammatory cells and stromal/adipocyte cells that mediate the inflammatory response, and these cytokines (e.g. IL-1, IL-6 and Tumour Necrosis Factor-alpha) are signals that stimulate tumour growth. Dietary lipids such as omega-6 fatty acids can independently stimulate inflammation by conversion to pro-inflammatory prostaglandins. The omega-3 and omega-6 fatty acids compete for the active sites on cyclo-oxygenase (COX) enzymes. There are two isoforms of COX, designated COX-1 and COX-2. COX-1 is a housekeeping gene that is expressed constitutively in many tissues. On the other hand, COX-2 is undetectable in most normal tissues but is induced by inflammatory and mitogenic stimuli. There is accumulating evidence that COX-2 is important in carcinogenesis.

The plant world is rich in inhibitors of cyclo-oxygenase. Compounds extracted from crabapple fruits have demonstrated activity in COX enzyme inhibitory and antioxidant bioassays[17] and alpha-viniferin, a trimer of reseveratrol, has an inhibitory effect of COX-2 and inducible nitric oxide synthase.[18] Animal studies have also demonstrated the inhibition of colon cancer from curcumin in turmeric[19] and inhibition of skin and breast cancer from carnisol in rosemary.[20,21]

Anti-cancer Effects of Phytochemicals

There is established evidence which relates the protective benefit of fruit and vegetable intake against cancers of the lung, colon, breast, cervix, oesophagus, oral cavity, stomach, bladder, pancreas and ovary.[22] Cancer is a disease resulting from genetic changes, and about 100 genes have been identified that code for oncogenes or tumour suppressor genes. Oncogenes are normal genes that form either growth factors (e.g. IGFs) or growth factor receptors (HER-2-neu). These genes normally turn on and off as part of the complex set of events underlying normal cell function. However, in cancer cells, mutations in the regulatory regions of these genes lead to amplified expression of multiple copies so that stimulation is an unrelenting and the cell grows in an unregulated fashion. Alternatively, a tumour suppressor gene is a gene for a protein that turns off cell growth and leads to apoptosis due to binding of the protein to elements in the nucleus. For example, recent animal studies have demonstrated the inhibition of intestinal tumour development by tart cherry anthocyanins.[23]

Phytochemicals found in fruits and vegetables can affect the above processes by several mechanisms. Free radical damage which induces oxidative stress can cause DNA damage, which in turn can lead to base mutation, DNA cross-linking, and chromosomal breakage and rearrangement. This damage may be limited by dietary antioxidants in fruits and vegetables through modulation of detoxification enzymes, scavenging of oxidative agents, stimulation of the immune system, hormone metabolism, and regulation of gene expression in cell proliferation and apoptosis.[24-26] Whole plant extracts may have more than one mechanism. Curcumin, for example, has been shown to have several anti-metastatic mechanims in hepatocellular carcinoma cells.[27]

Lycopene from Tomatoes and Tomato Products

Tomato products, including ketchup, tomato juice, and pizza sauce, are the richest sources of lycopene in the American diet, accounting for more than three-fourths of the total lycopene intake of Americans.[28] Several studies have linked the consumption of tomatoes and tomato products with a decreased risk of cancer and cardiovascular disease. The health benefits of lycopene have been attributed to its antioxidant properties, although other mechanisms of lycopene action are possible, including the modulation of intercellular communication, hormonal and immune system changes, and enhancement of gap junctional communication.[29] In breast cancer cells, lycopene can interfere with insulin-like growth factor 1–stimulated tumour cell proliferation.[30]

The relationship between lycopene intake and prostate cancer risk has been reported and supported by studies linking low plasma levels of lycopene with an increased risk.[31-34] Lycopene administration may reduce proliferation and increase apoptosis in human prostate tissue where lycopene is the predominant carotenoid.[35]

The anti-proliferative properties may extend to other types of cancer, including that of the colorectum,[36] and lycopene may inhibit cholesterol synthesis and enhance LDL degradation.[37,38] Several studies have established that the processing of tomato products into sauces, soups and juices increases the bioavailability.[39] The basis of a recent review of the functional properties of foods[40] and research from our laboratories has demonstrated that it is relatively simple to influence the circulating levels of lycopene with the administration of only 177

mL (6 fluid ounces) of mixed vegetable juice daily.[41]

Isothiocyanates from broccoli and other cruciferous vegetables

The consumption of cruciferous vegetables has been associated with a reduced risk of cancer of the lung, stomach, colon and rectum. The health benefits of cruciferous vegetables such as broccoli, Brussels sprouts, cabbage, and bok choy have been attributed to their high concentration of glucosinolates. The chemoprotective effect of indole-3-carbinol, a constituent of these vegetables, has been shown to have chemopreventive effects in mouse models of colon cancer.[42] These compounds are normally chemically conjugated to sugar residues and are stable. However, when the plant cell is crushed or chewed, myrosinase enzymes are activated and break these stabilized chemical structures to yield volatile and highly reactive compounds such as isothiocyanate. The body normally detoxifies itself in two steps so that it can get rid of the highly reactive compounds. Phase I enzymes add an electron to the compound and Phase II enzymes catalyse a reaction that links a sugar or sulfate residue on the activated toxin so that it becomes water soluble and is excreted in the urine. Isothiocyanates act as anti-carcinogens by inducing Phase II conjugating enzymes, in particular Glutathione S-tranferases (GSTs).[43]

It is very common for individuals to have genetic variation in these enzymes which are also the same system used to detoxify drugs. One common mutation is called a null mutation of the GSTM1 (Glutathione S-Transferase M1 type) enzyme that results in this enzyme being inactive. Under these circumstances, isothiocyanates persist in the circulation, leading to activation of other GST enzymes. The net effect is that the individual with the null mutation is more protected from cancer due to the inability of the body to rid itself effectively of isothiocyanate. In population studies, individuals with this null mutation have a significant reduction in the risk of colon cancer if they eat broccoli or other cruciferous vegetables regularly.[44]

Green Tea Polyphenols

Tea is one of the most popular beverages in the world and the consumption of tea has been associated with a decreased risk of developing cancer of the ovary[45], oral cavity,[46] colon,[47] stomach,[48] and prostate.[49] This beneficial health effect has been attributed to the catechins in tea: (-)-epicatechin (EC), (-)-epigallocatechin (EGC), (-)-epicatechin gallate (ECG) and (-)-epigallocatechin gallate (EGCG). Their biological benefits are due to their strong antioxidant and anti-angiogenic activity as well as their potential to inhibit cell proliferation and modulate carcinogen metabolism.[50,51]

Catechins account for 6-16% of the dry green tea leaves. During the manufacture of black and oolong teas, tea leaves are crushed to allow the polyphenol oxidase to catalyse the oxidation and polymerisation of catechins to polymers called theaflavins (2-6%) and thearubigins (20%). These polymers contribute to the characteristic bright orange-red colour of black tea. Between 3 and 10% of the catechins remain in black tea. The major fractions of black tea polyphenols called thearubigins have higher molecular weights and are chemically poorly characterized.

Garlic

Garlic contains allyl sulphides which in their volatile state contribute to the strong odour. The sulphur compounds inhibit cell proliferation of cancer cells, modulate cell cycle activity and interfere with hormone action in cancer cells. [52-55] Allicin is the major ingredient in crushed garlic and has been shown to inhibit the proliferation of human mammary, endometrial and colon cancer cells.[55] Chronic Helicobacter pylori disease is reduced with allium vegetable intake, and substantial *in vitro* anti-Helicobacter pylori effects have been shown for pure garlic oil, garlic powder and allicin, which suggest that they may be useful for *in vivo* clinical use against Helicobacter pylori infections.[56]

Soy Isoflavones

Soy protein is the highest quality protein found in the plant kingdom, and it is eaten by two-thirds of the world's population. Soy protein naturally contains isoflavones, primarily genistein and daidzein, phytoestrogens which act like very weak oestrogens or anti-oestrogens similar to raloxifene, and selective oestrogen response modifiers. In some tissues, soy acts as a mild pro-oestrogen (bone and brain) while in others it acts as an anti-oestrogen (breast and uterus). The evidence supporting an understanding of the cancer preventive potential of soy protein comes from a combination of evidence in cell culture, animals, and humans. Soy isoflavones bind with very low affinity (1/50,000 to 1/100,000 the affinity of estradiol) to the alpha-estradiol receptor, which mediates pro-oestrogen effects in the breast and uterus, but isoflavones and estradiol bind equally well to the beta-estradiol receptor, which mediates the effects of oestrogen on lipids, bones and brain.

In 1994, Messina et al reviewed 26 studies showing the effects of soy or soy isoflavones on eight cancer sites in animals.[57] A majority of the studies (17 of 26, or 65%) showed that soy may have protective effects. None of the studies indicated that soy increased tumour development. In addition, the studies of populations eating soy protein indicated that they had a lower incidence of breast cancer and other common cancers compared to populations such as the US population where soy foods were rarely eaten.[58] These studies provided only supportive evidence for a positive role of soy foods, since the diets of the populations eating more soy protein were also richer in fruits, vegetables and whole cereals and grains in comparison with the US diet. Soy protein isoflavones have been shown to influence not only sex hormone metabolism and biological activity but also intracellular enzymes, protein synthesis, growth factor action, malignant cell proliferation, differentiation and angiogenesis, providing strong evidence that these substances may have a protective role in cancer. [59]

Soy food intake has also been shown to have beneficial effects on cardiovascular disease, although data directly linking soy food intake to clinical outcomes of cardiovascular disease have

been sparse. A recent study among the participants of the Shanghai Women's Health Study, a population-based prospective cohort study of approximately 75,000 Chinese women, documented a dose-response relationship between soy food intake and risk of coronary heart disease, providing direct evidence that soy food consumption may reduce the risk of coronary heart disease in women.[60]

Interactions among Different Phytochemicals

Phytochemicals from different plants can interact to inhibit cancer cell growth (e.g. soy isoflavones and green tea catechins).[61,62] It has also been proposed that the additive and synergistic effects of phytochemicals in fruits and vegetables are responsible for their antioxidant and anti-cancer activities, and that the benefit of plant-based diets is attributed in part to the complex mixture of phytochemicals present in whole foods.[63-65] Clearly, no single antioxidant can replace the natural combination of thousands of phytochemicals that exist in whole foods. Given the history of the diverse intake of plant foods by mankind, it is sensible to encourage a diverse intake. The exact amounts of fruits and vegetables needed each day to minimise cancer risks are not known and will require a great deal of additional research. However, the evidence of the benefits of fruits and vegetables suggest that it is not premature to advise increased intake of a variety of colourful fruits and vegetables.

Selecting Foods by Colour

Humans and a few primate species have trichromatic colour vision so that they are able to distinguish red from green.[66] All other mammals have dichromatic vision and cannot distinguish between the two colours. One hypothesis for the evolution of this visual ability was that it conferred an advantage by enabling primates to distinguish red fruits from the green background of forest leaves. Today colours are still used to promote food choices and contrasting colours have been shown to be one of the key factors in food selection.[67] Most Americans eat only two to three servings of fruits and vegetables per day without regard to the phytochemical contents of the foods being eaten. Certain phytochemicals give fruits and vegetables their colours and also indicate their unique physiological roles. All the coloured phytochemicals that absorb light in the visible spectrum have antioxidant properties. In artificial membrane systems, it is possible to show synergistic interactions of lutein and lycopene in antioxidant capacity and there are well-known antioxidant interactions of vitamin C and vitamin E based on their solubilities in the hydrophilic and hydrophobic compartments of cells.

Table 1. Colour Code Groups of Fruits and Vegetables

Colour	Phytochemical	Fruits and Vegetables
Red	Lycopene	Tomatoes and tomato products (soups, juice, pasta sauce)
Red/Purple	Anthocyanins and Polyphenols	Berries, grapes, red wine
Orange	Alpha and Beta Carotene	Carrots, mangoes, pumpkin
Orange/Yellow	Beta-cryptoxanthin and Flavonoids	Cantaloupe, peaches, oranges, papaya
Yellow/Green	Lutein and Zeaxanthin	Spinach, avocado, honeydew
Green	Glucosinolates and Indoles	Broccoli, cabbage, cauliflower
White/Green	Allyl Sulphides	Leeks, onion, garlic, chives

A method for selecting fruits and vegetables based on colours keyed to the content of phytochemicals is a way of translating the science of phytochemical nutrition into dietary guidelines for the public.[68] It can also help consumers change dietary patterns to include more fruits and vegetables by including one serving from each of the seven colour groups each day as shown in the table below.

Although the colour method is superior to the current system of simply encouraging increased fruit and vegetable intakes, it does not account for actual phytochemical delivery to the consumer. Today, there is no labelling law that enables fruit and vegetable manufacturers to list the phytochemicals in their products. Further, fruits and vegetables are developed and preserved to transport them over long distances and extend their shelf life rather than for their flavour or nutritional content. Research in this area needs to continue on the more than 25,000 phytochemicals provided by fruits and vegetables. These important phytochemicals are widely distributed among different plant species, but the delivery of the phytochemicals and their effects on biomarkers relevant to health promotion and disease prevention need to be documented.

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