PHYTOCHEMICALS & CANCER

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ABSTRACT

Background: Although traditionally cancer has been fought with the usual armamentarium of chemotherapy and high doses of directed radiation, lately there has been more attention devoted to combating cancer through nutritive means. In particular, certain phytochemicals including some vitamins, some minerals and a wide range of other bioactive nutrients have been found useful in the physiological battle against cancer.

Objective: The objective of this article is to determine which vitamins, minerals and bioactive nutrients may be useful in combating cancer and to give therapeutic dosages of such when known.

Data Synthesis: The scientific literature is replete with research documenting the link between certain nutritional protocols and inhibition or protection against the disease of cancer. From the landmark article entitled *The Causes of Cancer* by Richard Doll and Richard Peto which was first commissioned as a report to the Office of Technology Assessment of the United States Congress to the American Cancer Society's Advisory Committee Guidelines on Diet, Nutrition and Cancer Prevention: *Reducing the Risk of Cancer with Health Food Choices and Physical Activity*, the nutritional literature continues to provide the necessary link for the clinician to justifiably advise patients regarding proper dietary habits in order reduce the patients risk of cancer.

Results: Although there has been much research regarding the relationship between vitamins, minerals and other bioactive phytonutrients and cancer and protection against cancer, not all of the literature supports a strong and convincing link between the nutrient and cancer protection. This article differentiates the convincing evidence vs. the probable and the possible evidence of the link between the nutrient and its inhibitive effect on cancer.

Conclusion: Certain vitamins, minerals and bioactive phytonutrients can be used as a first line of therapeutic defense against cancer before chemotherapy and radiation treatment is commenced. (*J Chiropr Med* 2002;1:91-96)

KEY INDEXING TERMS: Phytochemicals; Cancer; Vitamins; Minerals; Botanicals.

INTRODUCTION

A phytochemical is any substance that is derived from a plant source. Sometimes the term phytonutrient or phytoprotectant is substituted for the word phytochemicals. Phytochemicals may relate to any one of a number of vitamins, minerals or bioactive compounds produced by the plant.

DISCUSSION

Vitamins and Cancer

Although there has been much research regarding the relationship between vitamin intake and cancer, only a few vitamins have been documented to help reduce the risk of cancer. Many other examples of vitamin therapy have shown promise but yield equivocation upon literature reviews. For purposes of discussion, this section will focus on vitamin E, retinol, vitamin B-12, folic acid, vitamin C and the carotenoids.

One of the most well researched vitamins with respect to its association with cancer and cancer prevention is beta carotene. This vitamin is found in green leafy vegetables and fruits. Pumpkin, winter squash, cantaloupe, apricots, carrots, spinach and collard greens are rich sources of beta carotene. Alpha carotene can be found in carrots, pumpkin and avocado.

Subsets of the carotenoids include the xanthophylls, lycopene and cryptoxanthin. Of the xanthophylls, lutein is a major component and is largely found in spinach, kale and other greens. Lycopene is found in tomatoes, watermelon and guava. (1) Cryptoxanthin is found in persimmon, red peppers, pumpkin and mangos. (2) Probably the richest source of mixed carotenoids is refined red palm oil.

The carotenoids are widely found in plants and are the chemical component making up the pigment. The main carotenoid precursor of vitamin A is beta carotene. As is vitamin A, all the carotenoids are fat soluble com-

pounds. All told, there are over 600 classified carotenoids.

Vitamin C is a water soluble vitamin found in many fruits and vegetables, milk and potatoes. Specifically, citrus fruits are high in vitamin C, as are vegetables such as broccoli, cabbage, tomatoes and yams. Since vitamin C is both water soluble and heat labile, it tends to be lost in foods that are cooked or exposed to open air for long periods of time. The oxidized form of vitamin C is known as dehydroascorbic acid, whereas the reduced form of vitamin C is known as L-ascorbic acid. Both are easily destroyed when exposed to heat, oxygen or water.

Folic acid got its name because it is abundant in foliage. Hence folic acid can be found in green leafy vegetables as well as whole grain cereals. Another name for folic acid is pteroyl glutamic acid. Free folic acid is not physiologically active until it is reduced to dihydrofolic acid. The naturally occurring forms of folic acid include tetrahydrofolate, 5-methyl tetrahydrofolate and 10-formyltetrahydrofolate. All are important in the synthesis of purines, methionine, pyrimidines and glycine.

Another fat soluble vitamin which is found largely in vegetable oils is vitamin E. Vitamin E can be found in whole grains, wheat germ and nuts also. In nature the most widely distributed form of vitamin E is alpha-tocopherol. This form of vitamin E is especially prevalent in sunflower, safflower, olive and canola oil. Another vitamin E compound includes the tocotrienols. There are 4 isomers of both tocopherols and tocotrienols that are common in nature.

One of the most important actions of vitamin E is as an antioxidant. It is essential for proper neurological and immune function and can help to prevent red blood cells from lysing.

One of the strongest associations between vitamins and the reduction of risk of cancer involves beta-carotene in lung cancer. (3) When adjusted for tobacco smoking, there is still strong evidence that beta-carotene helps to reduce the risk of lung cancer in both males and females. This association extends also into the animal kingdom.

Carotenoids in general are believed to help protect against many forms of cancer. Although the relationship is not as strong as between beta-carotene and lung cancer, there is a suggestion of protection from the carotenoids against cancer of the esophagus, stomach, colon, rectum, breast and cervix. Probably the major

reason these carotenoids are helpful in protecting against cancer is because of their strong antioxidant capacity. They tend to be very capable of seeking out and neutralizing free radicals. In addition to their antioxidant capabilities, Vitamin A seems to be instrumental in promoting normal cell differentiation and thereby inhibiting cancerous aberrant cell growth. The third mechanism which may explain the effectiveness of vitamin A against cancer involves the ability of both beta and alpha-carotene to inhibit cell proliferation.

There appears to be a very strong relationship between vitamin C and the reduction and the risk for stomach cancer. Certain studies have shown that those patients who have died from stomach cancer have plasma vitamin C levels that were well below normal. Animal studies have shown that vitamin C tends to inhibit tumor formation. There is also a possible relationship between vitamin C and the reduction of the risk of mouth, pharyngeal, esophagus, lung, pancreatic and cervical cancer.

As with vitamin A, the research shows that vitamin C tends to be effective against cancer due to its strong antioxidant capacity and because it is widely abundant in the body's circulatory system and intercellular fluids. Vitamin C neutralizes free nitrites which can be used as a substrate in carcinogens. Finally, vitamin C enhances the immune system as well as aids in the resynthesis of connective tissue such as collagen.

There is some evidence that vitamin E may also protect against cancer. (4) Although the research literature is not as strong in documentation regarding the carotenoids versus lung cancer, there remains a possible link between the consumption of dietary vitamin E and the reduction in risk of both lung and cervical cancers.

Again, a major reason for the effectiveness of vitamin E against cancer is due to its intracellular antioxidant capacity. Vitamin E is one of the most important antioxidants found in the body's fat deposits. Therefore, it tends to prevent polyunsaturated fatty acids from becoming oxidized. If not for vitamin E, this oxidation of the polyunsaturated fatty acids would lead to the formation of malondialdehyde which may be a carcinogen. Another reason for the effectiveness of vitamin E is because it helps to keep selenium and carotenoids in a reduced state which make them more effective as antioxidants. Finally, vitamin E also tends to inhibit the formation of nitrosamines which are involved in some pro-cancerous reactions.

Folate may also be helpful in preventing or reducing the risk of cancer. In particular, folate may help to reduce the risks of colon and rectal cancers. (5) However, the research evidence is insufficient to make a firm conclusion.

Minerals and Cancer

For purposes of this discussion, we will limit our attention to 4 minerals and trace elements: calcium, selenium, iodine and iron. Of these there is strong empirical evidence that suggests that diets deficient in iodine tend to increase the risk of thyroid cancer whereas diets high in selenium tend to decrease the risk of lung cancer.

Of the four elements mentioned, calcium is by far the most abundant in nature. Calcium can be found in both animal and plant sources. The most abundant sources of calcium include dairy products and small fish. Like zinc, the absorption of calcium may be impeded with ingestion of oxalate-rich foods such as rhubarb and spinach or phytate-rich foods such as cereals and grains (especially wheat).

Selenium may be found in fish, meat and cereals. Selenium is probably most readily available in cereals but varies widely with the type of soil from which the grain is harvested.

Iron that is readily bound in the hemoglobin molecule is found only in animal sources such as meat, fish, sausage and foods made from blood byproducts. Non-haem iron can be found in plant products such as vegetables, cereals and pulses.

The most reliable sources of iodine can be found in seaweed and most seafood. Many countries add iodine to their table salt. The most important function of iodine resides in its ability to influence human metabolism at both the cellular and physiological level. Iodine is important in maintaining the integrity of the connective tissue.

With respect to physiological functions, iron plays a central role in cell metabolism and growth as well as being germane to various enzymatic reactions. Most iron found in the body is bound to proteins such as transferrin and ferritin, which tend to limit its ability in producing free radicals.

The role of calcium in the body is tied in largely with bone metabolism but is also involved with nerve and muscle activity. Calcium is also involved with cell proliferation and tends to be largely controlled by the pres-

ence or absence of vitamin D. Vitamin D helps to regulate the calcium/phosphorous ratio and subsequent balance in the body.

Although selenium by itself tends to be somewhat impotent as a metabolic regulator, when acting as a cofactor for glutathione peroxidase, it becomes a potent antioxidant. Glutathione peroxidase is instrumental in detoxifying the hydroxyl radical, which is one of the most damaging free radicals found in the body.

The recommended daily allowance for calcium is 800 mg. per day for the adult. This is increased to 1200 mg. per day for pregnancy and lactating women. Although there has been considerable debate with respect to the recommended daily allowance for selenium, over the past 10 years, the US National Research Council has recommended 75 micrograms for adult men and 55 micrograms for adult women. Again, the RDA for women is increased by 10 to 20 micrograms per day when pregnant or lactating.

The recommended daily allowance for iron in adult males is 10 mg, whereas adult females is 15 mg. The National Research Council recommends 30 mg per day of iron for pregnant females. However, other organizations recommend as high as 45 mg per day.

Finally, the recommended daily allowance according to the National Research Council for iodine for adult males and females is 150 micrograms. For pregnant females this daily allowance goes up to 175 micrograms and for lactating females 200 micrograms.

In areas where the daily intake of iodine is far less than 150 micrograms per day, goiter tends to be endemic. In areas where the daily average intake of selenium tends to be less than 20 micrograms per day, Keshan disease is endemic. This is a type of cardiomyopathy which is responsive to selenium supplementation. (6) The problem tends to be widespread in certain regions in China. Selenium deficiency is more prevalent in smokers than non-smokers. Selenium levels can be somewhat accurately construed through both blood analysis as well as toenail trace mineral analysis. Alternatively, selenium can have just as detrimental effect on the human body when taken in excess. Daily intake levels of 5 mg. or more may cause selenium toxicity, which can be lethal.

Over the past 2 decades, there has been much discussion regarding the relationship between intake of calcium and reduction of colo-rectal cancer. Although the possibility does exist and some citations can be found in support of this, the documentation tends to be equivo-

cal. (7) Likewise, there also appears to be some relationship between diets high in iron and an increased risk of liver and colo-rectal cancers. However, the research again appears to be equivocal.

With respect to selenium, there is more scientific evidence relating the intake of selenium with the reduction of incidence of lung cancer. Additionally, there is other evidence linking the protection of selenium against cancer in general. Comstock et al wrote of such protection in a 1992 issue of the *American Journal of Epidemiology*. (8)

The risk of thyroid cancer can be seen with both very low or very high intakes of iodine. The relationship is stronger with iodine deficiency than with iodine excess. The iodine deficient state tends to increase the risk of follicular cancer of the thyroid.

Other Bioactive Phytochemicals

Besides vitamins and minerals, there are other phytochemicals which are known to be bioactive and may be useful in the fight against cancer. These include the allium compounds, dithiolthiones and isothiocyanates, terpenoids, phytoestrogens, flavonoids, phenolic compounds, protease inhibitors, phytic acid, glucosinolates and indoles, plant sterols, saponins and chemicals found in various botanicals.

Allium Compounds

Some of the strongest scientific evidence exists between combating stomach cancer and the ingestion of allium compounds. These compounds can be found in many vegetables including scallions, chives, garlic and onions. The allium compounds contain sulfur in the form of diallyl sulphide and allyl methyl trisulphide. Garlic contains the amino acid allin which is enzymatically converted to allicin when the clove is crushed or cut. Garlic also contains allixin which is a phenolic compound. These allium compounds protect the stomach against cancer by inhibiting the bacterial conversion of nitrate to nitrite. They also have antibiotic properties which fight off the ulcer promoting bacteria known as *Helicobacter pylori*. There is much research that suggests that diets high in allium compounds are protective against stomach cancer. (9)

Dithiolthiones and Isothiocyanates

These compounds are found in cruciferous vegetables such as broccoli, brussel sprouts and cauliflower. The isothiocyanates include benzyl isothiocyanate, phenethyl isothiocyanate and sulforaphane. These com-

pounds are also sulfur containing with a chemical structure that is composed of a pentacyclic ring as well as an aromatic ring. They may be helpful in protecting against cancer by inhibiting enzymes that activate carcinogens or by inducing detoxifying enzymes.

Terpenoids

The most studied terpenoid is known as D-limonene which is found in the oil of the citrus fruit peel. In the US, D-limonene is used as a flavoring agent in certain beverages, baked goods, gelatins, puddings, ice cream and chewing gum. Terpenoids are believed to be active against cancer by enzymatically promoting glutathione transferase. (10)

Phytoestrogen

Phytoestrogens include the isoflavones and lignans. The isoflavones can be found in millet, sorghum and soybeans as well as other cereals and legumes. Lignans can be found in seeds, fruits, berries and grains. Both isoflavones and lignans are diphenolic compounds which tend to vary greatly in their structure.

The phytoestrogens may help to ward off cancer due to a variety of biological effects and may be protective against breast cancer (especially the isoflavones). Namely, phytoestrogens inhibit growth and are both antiviral and antiproliferative. Phytoestrogens get their name because they resemble human estrogen and can compete with receptor sites.

Flavonoids

Flavonoids consist of quercetin, myricetin and kaempferol and can be found in coffee, tea, cola, alcoholic beverages, fruits and vegetables. They are most widely found in fruits and vegetables. Quercetin is found in broccoli, squash, berries, tomatoes, potatoes, beans and onions. Kaempferol is found in endive, kale and radishes. Myricetin can be found in citrus fruits. All flavonoids tend to be potent antioxidants and are useful in chelating metallic ions. Plants use flavonoids to help protect them from viruses, fungi and as a repellent to keep animals from feeding on them. Of the flavonoids, quercetin may be helpful in inhibiting the proliferation of leukemia. Quercetin may also inhibit tumor production. Like the relationship between isoflavones and breast tumor inhibition, there is insufficient evidence which links quercetin intake and general tumor inhibition. (11)

Phenolic Compounds

In addition to allium, other phenolic compounds include caffeic, ferulic and ellagic acids. These are found in teas, wines, vegetables and fruits such as strawberries, blackberries and raspberries. Phenolic compounds may be helpful in inhibiting cancer by inducing certain detoxification systems. For instance, they may help to inhibit N-nitrosation reactions. Certain of these polyphenols may inhibit specified types of cancer. Ellagic and caffeic acids may inhibit cancerous tumors of the tongue. Ellagic acid by itself may also inhibit esophageal and skin tumors. (12)

Protease Inhibitors

Protease inhibitors are found largely in plant sources especially cereals such as oats, wheat, barley and rye and pulses (legumes) such as kidney beans, soybeans and chickpeas. Protease inhibitors can also be found in tofu. The structure of protease inhibitors involves long chain proteins consisting of at least 70 amino acids. As the name suggests, protease inhibitors tend to inhibit proteases by blocking the enzymes catalytic site. These compounds may be useful during the highly invasive phase of cancer.

Phytic Acid

Phytic acid is found in high quantities in seeds (especially sesame seeds), pulses (especially lima beans and soybeans), nuts (especially peanuts) and cereals. The other name for phytic acid which also helps to identify its chemical structure is inositol hexaphosphate. This bioactive compound works by altering intestinal absorption of specific minerals through forming insoluble salts with specific cations. This process may in turn help to inhibit cancerous cell proliferation.

Glucosinolates and Indoles

Glucosinolates can be found largely in cruciferous vegetables. Approximately 30% of the glucosinolates are found in the chemical structure known as glucobrassicine. Indoles are produced by the process of cooking and chewing glucosinolates. The potency of indoles may be adversely affected by various methods of harvesting and storing. There has been a great deal of popularization of the anticancerous effects of cruciferous vegetables. It is the glucosinolates in these vegetables that may be the effective agent. In particular, glucobrassicin and indole derivatives may be helpful in inhibiting the formation of tumors in the lung, breast, stomach and liver. (13) Most of these research studies have involved animals such as rats.

Plant Sterols

Plant sterols are found in vegetables and include: beta sitosterol, stigmasterol and campesterol. All are similar in structure to cholesterol. They pass through the GI tract largely unabsorbed and can influence both cholesterol absorption and metabolism. There may be a relationship between ingestion of beta sitosterol and reduction in colon cancer. (14) It is of particular interest that vegetarians tend to have a high level of beta sitosterol in their feces.

Saponins

Saponins are largely found in legumes, especially soybeans. Their chemical structure is known as an amphiphilic glycoside. The property that makes saponins unique is their ability to make foam when shaken vigorously yielding a high surfactant coefficient. Biologically, they tend to exhibit both cytotoxic effects as well as inhibit growth of a variety of cells. (15) They can also bind bile acids. A few studies have shown that saponins may reduce colon cancer as well as decrease the growth rate of cancerous DNA synthesis.

Botanicals

Certain botanicals may have other phytochemicals in them which tend to be anticarcinogenic. For instance, aloe vera is composed of a water-soluble chemical known as acemannan which may be a potent immunostimulant. Golden seal and barberry root may be helpful in fighting the leukopenic side effect of chemotherapy due to its inherent phytochemical known as berberine. (16)

Chaparral has been used as an anticancer herb and an antioxidant chiefly because of its inherent phytochemical known as nordihydroguaiaretic acid (NDGA). Dong quai, red and sweet clovers have historically been used to combat cancer due to a component they all have in common known as coumarin. In particular, red clover has been used in a popular folk remedy for cancer known as the Hoxsey formula. Green tea has been used to fight cancer and is probably effective due to its many component polyphenols. Finally, tumeric may be helpful as a powerful antioxidant and cancer inhibitor due to its active component curcumin.

CONCLUSION

Phytochemicals should be used in the treatment protocols of all nutritionally oriented physicians when combating cancer prior to and sometimes in conjunction with standard chemotherapeutic techniques and radia-

tion therapy. Although much research needs to be done in order to prove the exact efficacy of each one of the phytonutrients, many have shown much promise in the field of onocological therapeutics.

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