Cancer can legitimately be placed at the head of the list of public health dangers in America. For many types of cancer good treatment techniques exist, but for some of the most prevalent cancers in American society the treatment modalities available are either dangerous, ineffective or both. This fact, as well as economic considerations, has spurred substantial interest in means of cancer prevention. Epidemiological studies have suggested that one of the most important determinants of cancer risk for an individual is his or her diet; it is an important etiology in 30-60% of varieties of cancers (3). Different foods appear to have positive and negative influences on carcinogenesis; one of the most striking is the plant genus *Brassica*, the cruciferous vegetables (7).

Epidemiologic studies demonstrate a relationship between a diet high in cruciferous vegetables and an across the board decrease risk of endometrial cancer, tongue cancer, liver cancer, and cancer are only some of the types of cancer whose incidences appear to be negatively correlated to cruciferous vegetable consumption (5). Breast cancer and colorectal cancer are the two types of cancer in which this beneficial effect is most pronounced (4). A recent study in Spain found a trend of decreasing breast cancer incidence with increasing amount of cruciferous vegetables in an individuals diet (1). There is reason to believe that some of the healthful effects of a high cruciferous vegetable diet are due to the vegetables' relatively high fiber content or are simply due to increased consumption of vegetables period, but there are at least two considerations that indicate their is more to it. First, although other vegetables have been shown to be beneficial in reducing cancer risk as well, they do not do so to the same degree. Also, a diet high in non-cruciferous sources of fiber is associated with a dramatic decrease in colorectal cancer, but is not similarly related to decreases in incidence of other forms of cancer (7).

It appears that there are chemical compounds unique to cruciferous vegetables that serve to decrease an individual's chance of developing cancer. Although not entirely certain, it appears that these compounds may be glucosinoles found only in genus *Brassica* and the metabolic breakdown products of these glucosinoles, primarily isothiocyanates and inoles. Understanding these chemicals' nature and mechanism of action is key.

Indole-3-carbinol (I3C) is a product of the breakdown of a specific glucosinole found exclusively in cruciferous plants, glucobrassin. I3C has been shown to prevent many forms of cancer development in a number of animal studies, and has been proposed as a possible chemo-preventive agent for human breast and ovarian cancers. A study using liver cancer in mice showed that a long-term cruciferous rich diet, 1500ppm I3C for life, resulted in a dramatic decrease in carcinogenesis. Mice treated with I3C developed fewer tumors and smaller tumors than the control group on a restricted cruciferous diet. The investigators suggested that the I3C may be acting through estrogen-dependent pathways, although they did not suggest a mechanism for this action. An indole similar to I3C, brassinin, has had its chemo-preventive mechanism investigated more fully. It appears as though brassinin, and cruciferous indoles in general, acts in both the initiation and promotion phases of carcinogenesis (6).

A theory of one possible mechanism of cancer prevention deals with the relationship between cruciferous vegetables and glutathione S-transferase levels. Glutathione S-transferases have a number of functions in the body; their ability to reduce organic hyperoxides and catalyze electrophile-neutralizing reactions serves to protect DNA from damage. It was found that a diet rich in Brussels sprouts, 300 grams per day, swiftly elevated glutathione S-transferase in blood.

This study was done in human subjects, and limited in both sample size and duration, so the logical next step to look at decreased carcinogenesis has not been done. However, the investigators noted that increased glutathione S-transferase levels did not seem to be accompanied by any negative side effects and that it provided a mechanism by which a reasonable dose of cruciferous vegetables might act to reduce cancer risk in humans (2).

Another study of the anti-carcinogenic effects of cruciferous vegetables, also using Brussels sprouts, began with the conjecture that cruciferous vegetables act by reducing oxidative DNA damage. To study this in vivo they collected the urine of a high-cruciferous group and measured levels of 8-oxo-7,8-dihydro-2'deoxyguanosine (8-oxodG), a product of oxidative DNA damage. They found that the high-cruciferous diet resulted in much lower levels of 8-oxodG, evidence that some compound within the cruciferous vegetables was acting to decrease oxidative DNA damage. The investigators posited that glucosinoles within the vegetables were preventing peroxidation of human microsomes. This study provided experimental evidence to corroborate epidemiological findings and, secondarily, proposed a conceivable mechanism of action (8). There is corroborating evidence from other researchers that isothiocyanates and indoles counteract the carcinogenic properties of nitrosamines and polycyclic aromatic hydrocarbons, both relatively common environmental genotoxins.

Isothiocyanates, a second group of common products of glucosinole breakdown, have been shown to block tumor production in animal models. They appear to work through two complementary mechanisms: a suppression of carcinogen activation and a stimulation of the enzymes used by the body to detoxify electrophilic metabolites. Phase I, he inhibition of carcinogen formation is accomplished by both down regulating the levels of carcinogen forming enzymes and decreasing the effectiveness of those enzymes. The second phase, induction of enzymes like glutathione transferases, acts on the metabolites formed during phase I; the carcinogens are destroyed or otherwise rendered incapable of damaging DNA (9)

Surprisingly, there is experimental evidence that cruciferous vegetables may have carcinogenic properties. Compounds which have mutagenic effects are generally considered to be carcinogens; the untreated juice of cruciferous vegetables was found to induce genetic mutations in both bacterial and mammalian cells. Separating the juice into its constitutive parts identified the glucosinoles as the primary culprits in mutagenesis. The flavonoid/phenol portion of the juice also had mutagenic properties, but much less than the glucosinoles. This data, along with the fact that vegetables containing flavonoids and phenol compounds, but not containing glucosinoles, did not have similar mutagenic properties, strongly suggests that glucosinoles or their breakdown products are the culprits.

Interestingly, the mutagenic properties of the cruciferous vegetable glucosinoles were modified by two treatments. Acidification of the compounds, as would be done in the normal progression of ingested food through the gastro-intestinal system, decreased the mutagenic effects by approximately 25%. Heating the glucosinole compounds to 100 degrees Celsius, to simulate boiling or steaming vegetables, marginally increased the mutagenic effects (4).

The proposed mechanism of action by which glucosinoles induce mutagenesis is through action of glucosinole breakdown products. Glucosinoles break down to form isothiocyanates and inole compounds. Of these, it appears that the isothiocyanates are the compounds that cause cellular DNA damage. Differences in the genotoxicity of different varieties of cruciferous vegetables might be due to differences in the type of glucosinoles that they contain and the correspondingly different types of isothiocyanates that they produce (4).

The possibility that isothiocyanates may have carcinogenic properties is particularly troubling in light of the moves to use synthetically produced cruciferous compounds as chemopreventive drugs. It seems risky to consider giving patients large quantities of isothiocyanates when the exact nature of the isothiocyanates produced by glucosinole breakdown is not entirely known. It is certainly possible that isothiocyanates have properties that are both carcinogenic and chemo-preventive. It is also possible, and even likely, that it may be that certain doses of isothiocyanates are healthy and larger doses are harmful. The isothiocyanate dosage from a "dietary intake dose", that amount consistent with an un-supplemented cruciferous rich diet, might be the ideal at which beneficial effects are maximized and possible harmful effects are minimized. Loading patients with pills containing synthesized isothiocyanate, or isothiocyanate precursors, might push the dosage into an unhealthful realm.

In light of experimental results that are compelling, but not entirely unambiguous, it is reasonable, particularly for clinical purposes, to revert to the epidemiological findings. For reasons largely unknown, through mechanisms predominantly undescribed, a high-cruciferous vegetable diet seems to reduce an individual's risk of developing a broad spectrum of cancers. The few troubling reports on the carcinogenic properties within cruciferous vegetable juice do not have any correlate in the population and without that the information is intriguing, but not particularly worrying.

An area in which a deeper understanding of the mechanism of action of cruciferous vegetables is important is in drug design. The desire for a pseudo-magical pill that stops cancer is a powerful engine pushing investigation into chemo-preventive compounds found in nature, but it is necessary to curb investigative urgency with scientific caution. Before designing drugs based on compounds found within cruciferous vegetables it is absolutely necessary to identify exactly what compounds are beneficial, which, if any, are harmful, and what doses are optimal.

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