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Commentary

Broccoli sprouts as inducers of carcinogen-detoxifying enzyme systems: Clinical, dietary, and policy implications

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Cancer is the second leading cause of death in the United States; it accounts for nearly one-fourth of annual deaths (1). Although the rates of some cancers have been declining, rates of others have increased. Thus, despite advances in early detection and treatment, overall death rates from cancer have remained largely unchanged since the early 1970s, suggesting the need for a stronger research focus on prevention (2). Approaches to prevention necessarily include smoking cessation and dietary changes, because each is believed to contribute to about one-third of annual cancer deaths (3). For two decades, dietary advice to prevent cancer has emphasized fruit and vegetable consumption (4), and recent recommendations, such as those listed in Table 1, give highest priority to consuming plant-based diets (5, 6). Such advice is entirely consistent with recommendations for prevention of heart disease and other diet-related chronic diseases (4). It is supported by substantial, increasing, and extensively reviewed evidence linking intake of plant foods to impressive reductions in cancer risk at several major sites (6–11). On the basis of this evidence, researchers recently have estimated that plant-based diets prevent 20% (6) to 50% (11) of all cases of cancer.

Epidemiologic and animal studies have associated certain food plants with pronounced reductions in cancer risk. Among such plants are cruciferous (mustard family) vegetables of the genus *Brassica*: broccoli, cabbage, cauliflower, and Brussels sprouts, among others. National committees have recommended consumption of these vegetables for cancer prevention since the early 1980s (12). What characteristics of these vegetables might protect against carcinogenesis? Fahey *et al.* (13) directly address this important question. *Brassica* vegetables contain little fat, are low in energy, and are sources of vitamins, minerals, and fiber—all aspects linked to cancer protection. They also contain a large number of phytochemicals, some of which protect against carcinogenesis in various *in vitro* and animal testing systems (11). Table 2 summarizes the principal attributes and components of cruciferous vegetables that singly or together might protect against carcinogenesis.

The research of Fahey *et al.* (13) aims to identify specific phytochemicals in *Brassica* vegetables that may confer protection and the mechanisms by which they do so. The hypothesis underlying this work is that certain phytochemicals might raise the activity of enzyme systems that detoxify carcinogens. Several enzyme systems oxidize, reduce, or hydrolyze (phase 1) and then conjugate or otherwise affect (phase 2) drugs, metabolites, carcinogens, and other toxic chemicals, thereby increasing their polarity and excretability. Phase 1 enzymes activate or deactivate carcinogens, depending on the experimental conditions. Phase 2 enzymes are more likely to detoxify. For 20 years or more, consumption of cruciferous vegetables has been known to induce enzyme detoxification in experimental systems (12).

Such observations have led Paul Talalay and his colleagues (14–16) to conduct an elegant series of studies on the effects of cruciferous vegetable extracts on phase 2 enzyme induction and animal tumorigenesis. They have developed an *in vitro* assay to distinguish bifunctional phytochemicals that induce both phase 1 and phase 2 enzyme systems from monofunctional phytochemicals that induce only phase 2 enzymes. They then used this assay to demonstrate that *Brassica* vegetables are particularly rich sources of monofunctional phase 2 inducers (14) and to identify the isothiocyanate sulforaphane as the principal phase 2 inducer in broccoli extracts (15). They also have demonstrated that sulforaphane is a dose-related inhibitor of carcinogen-induced mammary tumorigenesis in rats (16).

These impressive accomplishments now have been extended to identify phase 2 inducer activity in sprouts of broccoli as well as in mature plants. Most of this activity derived from the glucosinolate precursor of sulforaphane, glucoraphanin. Because no net synthesis of phase 2 inducers occurs after sprouting, their concentration decreases as the plant grows. Extracts of broccoli sprouts contain 10–100 times the phase 2 inducer activity of mature broccoli plants and are more efficient inhibitors of rat tumorigenesis. In contrast, mature broccoli also contains significant amounts of indole compounds that induce phase 1 as well as phase 2 enzymes. Thus, sprouts would appear to offer at least two anticarcinogenic advantages over mature broccoli: they contain higher concentrations of inducers, and the inducers mainly affect phase 2 enzyme systems. On this basis, Fahey *et al.* (13) conclude that small amounts of cruciferous vegetable sprouts may be just as protective against cancer as larger amounts of mature plants of the same variety.

These studies leave no doubt that sulforaphane does indeed induce phase 2 enzymes and inhibit carcinogenesis under these conditions. At issue, however, is the clinical significance of induction of such enzyme systems by single phytochemicals. Both phase 1 and phase 2 systems are highly multifunctional and inducible by a wide variety of dietary compounds. Food plants have evolved to contain thousands of chemicals that act as protective pesticides against infection or predation (17), and humans may consume as many as 10,000 of these compounds and their metabolic products when eating vegetables. The Ames group (17) has identified 49 such compounds in cabbage, among them several that have been tested and found mutagenic or carcinogenic in animal test systems. Table 2 identifies the classes of phytochemicals in cruciferous vegetables that contain at least one compound that has proved mutagenic or carcinogenic in such tests. Thus, cruciferous and other vegetables contain some phytochemicals that are carcinogenic and others that are anticarcinogenic in test systems.

This confusing situation is complicated further by the ability of both phase 1 and phase 2 enzyme systems to inactivate some carcinogens, but activate others, depending on circumstances (18). Chemicals that induce activating enzymes also will induce activation of any other compounds present that are metabolized by the same system; the same is true of substances that

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Table 1. American Cancer Society guidelines for diet and cancer prevention (5)

Choose most of the foods you eat from plant sources.
Eat five or more servings of fruits and vegetables each day.
Eat other foods from plant sources, such as breads, cereals, grain products, rice, pasta, or beans several times each day.
Limit your intake of high-fat foods, particularly from animal sources.
Choose foods low in fat.
Limit consumption of meats, especially high-fat meats.
Be physically active: achieve and maintain a healthy weight.
Be at least moderately active for 30 minutes or more on most days of the week.
Stay within your healthy weight range.
Limit consumption of alcoholic beverages, if you drink at all.

induce inactivation. This dual nature of the enzyme systems, the vast number of compounds that can induce them, the presence in broccoli of chemicals that induce both activation and inhibition of carcinogenesis, and the complexity of the interactions among food phytochemicals and enzyme systems, constitute the basis of ongoing debates as to whether sulforaphane or any other single phytochemical or nutrient can explain the cancer-protective effects of cruciferous vegetables (19–21).

Fortunately, the dietary implications of this work are less complicated. The precise role in carcinogenesis of specific vitamins, minerals, fiber, and phytochemicals may be uncertain, but the overall anticarcinogenic properties of vegetables clearly outweigh any effects of their constituent carcinogens or carcinogen-inducers. The value of eating more vegetables in general, and *Brassica* vegetables in particular, is well supported by current evidence if for no other reason than this food group is a principal source of antioxidant vitamins; vegetables provide more than 80% of the carotene, 50% of the vitamin C, and 25% of the folate in the American food supply (22).

Dietary recommendations for prevention of cancer and other chronic diseases always have emphasized the value of consuming a variety of plant foods (4). Each vegetable contributes nutrients, fiber, and phytochemicals, but in varying amounts and proportions. Fahey *et al.* (13) found an 8-fold variation in phase 2 inducer activity among different samples of fresh broccoli, a variation that was independent of appearance or growing conditions. Broccoli may be especially rich in sulforaphane, but tomatoes are especially rich in lycopenes, peppers in carotenoids, and onions and garlic in allium compounds—all demonstrably protective against carcinogenesis (11).

Table 2. Potentially anticarcinogenic attributes and components of broccoli and other cruciferous vegetables (9, 11)

Energy and macronutrients
Low fat
Low energy
Micronutrients
Vitamin A
Vitamin C
Vitamin E
Folic acid
Selenium
Fiber
Phytochemicals
Carotenoids
Coumarins*
Dithiolthiones
Flavonoids*
Glucosinolates*
Indoles†
Isothiocyanates*
Phenols*
Terpenes

*Includes at least one compound identified as carcinogenic in test systems (17, 27, 28).
†Not present in sprouts (13).

President George Bush did not like broccoli (23); the mass appeal of broccoli sprouts is even less certain. My local health food store sells cruciferous sprouts of cabbage, radish, and mustard, but not yet broccoli; broccoli sprouts taste like milder versions of the mature vegetable and are slightly pungent or peppery. The store does offer dessicated broccoli in the form of 500-mg supplements labeled as containing 200 μg sulforaphane; 50 such tablets cost $14.70.

Price considerations aside, supplements confer little advantage. Fresh vegetables provide a higher content of vitamin C, folic acid, and fiber, and a balance of phytochemicals that favor overall protection against carcinogenesis. The full range of nutrients contained in foods must be present to detoxify carcinogens; iron, niacin, and riboflavin, for example, are essential cofactors in phase 1 and phase 2 enzyme systems. Just as single-nutrient approaches to cancer prevention have yielded disappointing results, single phytochemical approaches are likely to prove equally disappointing and are not recommended (5, 6).

The policy implications of this research also seem quite straightforward. Policies are needed to promote consumption of vegetables among a greater proportion of the population. Recent data suggest that the average American consumes slightly more than two standard half-cup servings of vegetables (other than white potatoes) daily; at least 10% of the population reports consuming less than one daily serving of any vegetable whatsoever (24). Although broccoli and cabbage rank among the top 10 vegetables purchased in supermarkets (25), and U.S. annual production (though not necessarily consumption) of fresh broccoli rose from 0.8 to 4.1 pounds per capita from 1973 to 1997 (26), this quantity translates to just 5 g per day per capita. Thus, the current situation leaves considerable room for improvement. From the standpoint of public health policy, existing data are more than sufficient to promote greater consumption of broccoli and its sprouts along with other vegetables. Educational campaigns to encourage fruit and vegetable consumption have achieved some success, but a greater range of policies and programs targeted to food producers as well as to consumers might prove more effective in raising consumption levels (4).

From the standpoint of cancer research policy, information about the role of each nutrient and phytochemical is of vital interest; such information may well explain why diet-related cancer risks vary across different sites and among individuals and populations. The effects of single anticarcinogenic phytochemicals, however, no matter how well characterized, cannot be understood in isolation, just as the anticarcinogenic effects of single nutrients cannot be understood except as part of an overall dietary pattern. Dietary patterns, of course, are difficult to study. If research to date has focused on the effects of isolated nutrients and phytochemicals, it is because such systems are far more amenable to investigation. Debates about the significance of the effects of sulforaphane on cancer risk are best interpreted as evidence of the need for high-quality research on the health effects of dietary patterns and their determinants—behavioral, environmental, economic, and cultural—as well as on the scientific basis of these relationships.

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