Anticancer Properties of Fruits and Vegetables

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Routine or habitual consumption of fruits and vegetables has been strongly associated with reduced risk for many of the common cancers (Steinmetz and Potter, 1991). The strongest evidence pertains to reduced risk for cancers of the mouth and pharynx, esophagus, lung, stomach, and colon. A moderately strong case can also be made for cancers of the breast, pancreas, and bladder. For other cancers, data are not sufficient to draw a conclusion on the effects of fruits and vegetables (American Institute for Cancer Research, 1997). Available scientific evidence suggests that some components of fruits and vegetables inhibit cancer; therefore, experiments have been conducted to pinpoint which foods provide the most benefit. With the increased ability to isolate and structurally identify phytochemicals in fruits and vegetables, cancer researchers have tested everything from fresh or freeze-dried fruits and vegetables to highly purified agents for cancer prevention. Both cell culture and in vivo studies in animal cancer models have solidly seconded data from human population studies. This paper will review some of the epidemiologic evidence for protection against the development of cancer in populations that consume fruits and vegetables. Also, the four basic mechanisms by which elements in foods can reduce the risk for cancer will be explored using data from animal carcinogenesis models.

THE EVIDENCE FOR FRUITS AND VEGETABLES AS CANCER PREVENTIVES IN HUMANS

Few studies in humans have evaluated the effect of consuming fruits and vegetables on cancer risk, and most of the available data come from case-control studies where eating patterns in people with cancer were compared with those of control subjects without cancer. One of the problems in assessing the effects of fruit and vegetable intake is the wide variety of these foods available. In a recent report of the expert panel assembled by the American Institute for Cancer Research (1997), a protective role for fruit and vegetable intake was ascribed for four tumor sites: oral-pharynx/esophagus, lung, stomach, and colon. The report inferred that available data are also strong supporting reduced risk for pancreas, breast, and bladder cancer in consumers of fruits and vegetables, and concluded that no increase in cancer risk has been reported for habitual consumers of fruits and vegetables at any tumor site. This is taken in context of concerns that minor contaminants such as fertilizers and pesticides may *potentially* pose a risk. The available evidence supports claims that fresh fruits and vegetables, when properly harvested, processed, and stored, help reduce risk for certain forms of cancer.

MECHANISMS BY WHICH FRUITS AND VEGETABLES REDUCE THE RISK FOR CANCER

Basic research has illuminated four potential mechanisms by which components in fruits and vegetables act to prevent cancer. These are reflected in our understanding of the process of chemical carcinogenesis and factors that influence the different phases of the process. The process of "initiation" conceptualizes the earliest aspects of cancer induction. Initiation refers to the immediate events surrounding the interactions between carcinogens and DNA that result in heritable mutations. Promotion and progression are terms that apply to the later phases of carcinogenesis, distinguished by clonal expansion of genetically altered cells and their eventual extrusion and metastatic spread to other organs. In terms of preventing cancer, two concepts are important at this early phase of the carcinogenic process: interception of DNA-reactive elements and activation and detoxification of potential carcinogens. In later stages, food components may interfere with the proliferation of clonal altered cells or disrupt the biology of the tumor in such a way that further growth or metastasis is impeded (Fig. 1).

Although the statement cannot be applied to all phytochemicals, compounds that are high in antioxidant potential are efficient interceptors of DNA-reactive elements (Malone, 1991). Generally, this refers to the electrophilic nature of chemical carcinogens. Being deficient in electrons, most mutagens/carcinogens are attracted to electron-rich sources in the cell. In terms of cancer development, DNA, RNA, and proteins have the highest nucleophilic potential to interact with an electrophile. Formation of stable bonds between the mutagenic agent and portions of nucleoprotein leads to adduct formation. Adduction of DNA is considered to be the sometimes repairable event that starts the carcinogenic process. Among the chemicals in fruits and vegetables, several have outstanding potential as antioxidants. Strong evidence exists that one class in particular, the plant phenolics, can prevent DNA adduction, presumably by presenting alternative targets for attack by carcinogens (Newmark et al., 1984; Teel and Castonguay, 1992). Plant phenolics are ubiquitous in the plant kingdom. Several have been tested for anticarcinogenic potential. For example, caffeic and ferulic acids prevent lung cancers in mice (Wattenberg, 1992). Among the more potent of these agents is the compound ellagic acid, found abundantly in strawberries (*Fragaria ×ananassa* Duch.) and raspberries (*Rubus* sp.). Ellagic acid strongly inhibited esophageal cancer when tested in rats (Mandal and Stoner, 1990). Among polyphenolic compounds, the catechins and related compounds in green tea are by far the most potent anticarcinogenic antioxidants yet tested (Chen, 1992). A partial list of the organ sites in which green tea has shown promising activity for cancer prevention is shown in Table 1. Green tea [*Camellia sinesis* (L.)] infusions or the extracted polyphenol fraction from green tea is active in all phases of carcinogenesis. This distinguishes the tea polyphenols from other plant phenols in that application of green tea infusions or polyphenolic fraction even after carcinogenic insult has occurred (i.e., postinitiation) is highly effective, especially in the case of experimentally induced skin cancer (Dreosti et al., 1997).

Another mechanism by which plant components can prevent

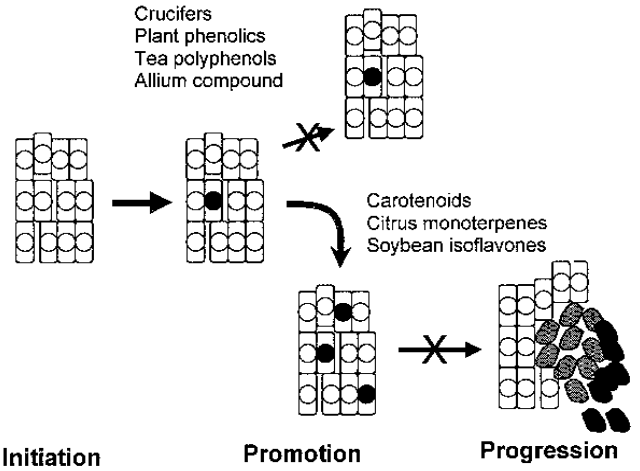

Fig. 1. Fruit and vegetable components influencing the process of carcinogenesis. Some plant compounds can interact with the metabolic activation of carcinogens and are more likely to influence the initiation phase of cancer. Others influence latter events involving the progression of initiated cells towards cancer.

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cancer in the early phases of carcinogenesis is through modulation of carcinogen metabolism (Fig. 2). A wealth of research has focused on chemicals in crucifers and *Allium* sp. vegetables that modify carcinogenesis by this mechanism. Isothiocyanates, found in cabbage (*Brassica oleracea* L. Capitata Group), broccoli (*Brassica oleracea* L. Botrytis Group), and cauliflower (*Brassica oleracea* L. Botrytis Group), inhibit cancer of the esophagus, lung, and colon in experimental animals (Chung et al., 1996). Extensive research in the metabolism of these compounds indicates that they are efficient modulators of carcinogen activation and detoxification. Current data support the observation that chemopreventative activity of isothiocyanates increases with chain length (Hecht et al., 1996). The most likely reason is that the long chain forms are more efficient substrates for the enzymes involved in carcinogen metabolism.

Members of the *Allium* genus, including garlic (*A. sativum* L.), onions (*A. cepa* L.), shallots (*A. cepa* L.), and chives (*A. schoenoprasum* L.), contain organosulfur compounds responsible for the odor and taste of these vegetables (Fenwick and Hanley, 1985). They are also highly reactive biologically, influencing both Phase 1 (carcinogen activation) and Phase 2 (carcinogen detoxification) enzymes. Thus, the volatile and water-soluble sulfur compounds from these vegetables are potent chemopreventives in animal models. Like the compounds in crucifers, agents in *Allium* sp. can modify the activation of carcinogens. Our laboratory has utilized a well-characterized animal model for colon cancer induced by the alkylating carcinogen azoxymethane. Azoxymethane and its precursor, dimethylhydrazine, are metabolically activated by the P450 cytochrome system, and specifically by the isoform CYP2e1. This isoform catalyzes the metabolism of a number of potentially important carcinogens (Yang et al., 1994). Marked suppression of CYP2e1 is associated with inhibition of carcinogenesis in several systems. Our laboratory has found that diallyl sulfide, one of the garlic volatiles, strongly inhibits colon cancer and esophageal cancer. Interestingly, both tumor models utilize carcinogens metabolized by CYP2e1 (Wargovich, 1992; Wargovich and Imada, 1993). Sulfur compounds from garlic and onion also stimulate carcinogen-detoxifying enzymes, such as glutathione-S-transferase, but administration of garlic compounds after carcinogenesis has been initiated is only partially effective, suggesting that these agents are effective during the period of carcinogen metabolism (Sparnins et al., 1988).

The last way in which fruits and vegetables can impact the cancer process is by modifying the behavior of cancer cells. In this situation a cancer cell may require abnormal stimulation of certain genes, leading to the production of growth factors that enable the cell to grow without normal cellular restraints. One of the first events discovered in cancer cells that distinguishes them from normal cells is the activation of oncogenes. Oncogenes are normal cellular genes that are "turned on" in the cancer cell and allow it to escape factors that regulate cell growth. The *ras* oncogene is one of the most frequently mutated genes in human cancers. As many as 30% to 50% of all cancers harbor a *ras* mutation.

Monoterpenes are a class of volatile chemicals found in many plants. Citrus fruits contain many monoterpenes and one of the most intensively studied compounds is limonene, which is found in oranges [*Citrus sinensis* (L.) Osbeck], lemons [*Citrus limon* (L.) M.L. Burm.)], and limes [*Citrus aurantifolia* (L.) Swingle]. Limonene inhibits the formation of mammary cancer when fed to rats (Elegbede et al., 1984). More importantly, this monoterpene regresses mammary tumors after they have become established in the rat (Haag et al., 1992). Early studies suggested that limonene is involved in the repression of the mutated *ras* oncogene. This implies that some monoterpenes may alter the course of tumors even in the later stages of their development. A metabolite of limonene, perillyl alcohol, is also found in nature, and has been isolated from hops (*Humulus lapulus* L.), lavender (*Lavandula angustifolia* Mill.), and cherries (*Prunus* sp.). Studies in our laboratory have focused on the chemopreventive properties of perillyl alcohol in a hamster model for pancreatic cancer. Cancer of the pancreas is one of the most indolent of human tumors and survival is abysmally low. Unique to the disease is the fact that 90% to 95% of pancreas tumors harbor mutations in the *ras* oncogene. In a pilot study we have evaluated the chemopreventive effects of perillyl alcohol in Syrian Golden hamsters treated with the pancreatic carcinogen bisoxopropylnitrosamine. Diet supplemented with 2% perillyl alcohol markedly reduced microscopic foci of pancreatic carcinoma in hamsters (Monotoya et al., 1997). Follow-up experiments are being done to determine whether the monoterpene treatment affected the status of the *ras* mutations induced by bisoxopropylnitrosamine in these tumors.

Table 1. Effects of tea on experimental cancer.

Organ site	Tea preparation	Main effect	Reference
Esophagus	Green tea	Moderate inhibition	Han and Xu (1990)
Lung	Green tea Black tea	Strong inhibition	Landau et al. (1998)
Colon	Green tea Black tea	Preneoplasias inhibited	Xu et al. (1996)
Skin	Green tea Black tea	Strong inhibition	Katiyar et al. (1994)

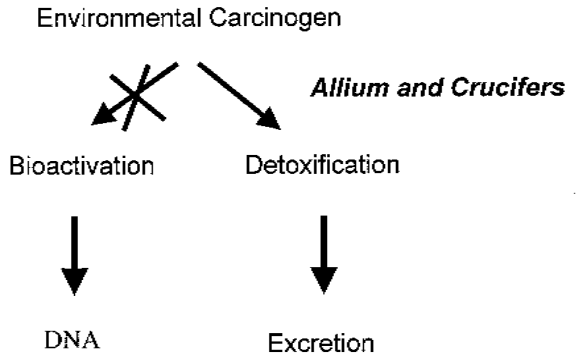

Fig. 2. Detoxification pathways are stimulated by *Allium* and cruciferous vegetables

The most recent development in the search for anticarcinogenic substances in fruits and vegetables involves the identification of antiinflammatory compounds that influence the generation of prostaglandins. Prostaglandins are mediators of pain, inflammation, and swelling produced from arachidonic acid by the enzyme cyclooxygenase (Marnett, 1992a). Drugs that inhibit cyclooxygenase have been strongly linked to reduced risk for colon cancer and other tumors (Marnett, 1992a). Collectively, these compounds are termed nonsteroidal antiinflammatory drugs. Representative examples include aspirin, ibuprofen, and related substances. Do fruits and vegetables contain similar compounds? Are they contributory to the reduced risk observed when fruits and vegetables are routinely consumed? The answers remain to be revealed, but several candidates are already known. These include resveratrol from red grapes (*Vitis* sp.), curcumin from turmeric (*Hydrastis canadensis* L.), green and black tea [*Camellia sinensis* (L.) Kuntze] polyphenols, and certain flavonoids in onions and rosemary (*Rosmarinus officinalis* L.).

SUMMARY

Fruits and vegetables in the daily diet have been strongly associated with reduced risk for the major forms of cancer afflicting high-risk countries such as the United States. In populations across the world where intake of these foods is high, the prevalence of the most common cancers is lower. Basic research into the mechanisms that explain how fruits and vegetables provide cancer prevention goes well beyond the notion that these foods provide only a rich source of dietary fiber. Some components of fruits and vegetables are certainly strong antioxidants and function to modify the metabolic activation and detoxification/disposition of carcinogens, or even influence processes that alter the course of the tumor cell. Further research will continue to pinpoint the active and cancer-preventive elements of the diet. Current research

should provide a dietary prescription for the next decade, and influence the development of designer produce enriched in the cancer prevention attributes provided by nature.

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