Allium Vegetables and Organosulfur Compounds: Do They Help Prevent Cancer?

Franca Bianchini and Harri Vainio

Unit of Chemoprevention, International Agency for Research on Cancer, Lyon, France

Allium vegetables have been shown to have beneficial effects against several diseases, including cancer. Garlic, onions, leeks, and chives have been reported to protect against stomach and colorectal cancers, although evidence for a protective effect against cancer at other sites, including the breast, is still insufficient. The protective effect appears to be related to the presence of organosulfur compounds and mainly allyl derivatives, which inhibit carcinogenesis in the forestomach, esophagus, colon, mammary gland, and lung of experimental animals. The exact mechanisms of the cancer-preventive effects are not clear, although several hypotheses have been proposed. Organosulfur compounds modulate the activity of several metabolizing enzymes that activate (cytochrome P450s) or detoxify (glutathione S-transferases) carcinogens and inhibit the formation of DNA adducts in several target tissues. Antiproliferative activity has been described in several tumor cell lines, which is possibly mediated by induction of apoptosis and alterations of the cell cycle. Allium vegetables and organosulfur compounds are thus possible cancer-preventive agents. Clinical trials will be required to define the effective dose that has no toxicity in humans.

Key words: Allium, cancer prevention, chemoprevention, garlic, organosulfur compounds, vegetables.

The Allium genus includes approximately 500 species, the most widely used of which are onions (Allium cepa), garlic (Allium sativum), leeks (Allium porrum), chives (Allium schoenoprasum), and shallots (Allium ascalonicum). Garlic is widely cultivated and consumed worldwide, and its beneficial effects have been known for thousands of years. It has been considered to increase longevity and to confer stamina and physical strength, and it has been used empirically as a vermifuge, antiseptic, antimicrobial, antipyretic, and analgesic. The scientific community has now become interested in the pharmacologic properties of Allium vegetables and their chemical constituents, particularly with regard to their effects on the cardiovascular system and in the prevention of cancer. Garlic has antihypertensive and antiarrhythmic properties and exerts an antithrombotic effect through fibrinolytic activity and the reduction of platelet aggregation. Ingestion of garlic has also been reported to lower the concentration of triglycerides, cholesterol, and low-density lipoproteins and to increase the concentration of high-density lipoproteins in blood. These findings suggest that garlic has a preventive effect against atherosclerosis and its complications, including stroke, myocardial infarction, and thrombotic disorders. The findings in relation to cancer prevention that have been accumulated over the last 20 years are summarized here.

We performed a systematic Medline search of the published literature on epidemiologic studies involving the relationship between consumption of Allium vegetables—garlic, onions, and leeks—and neoplasms/tumors. For the animal studies and for studies on mechanisms of action, we conducted searches for review articles. These lists of references were then updated using references from review papers and original research articles.

Active Compounds in Allium Vegetables

Fresh garlic contains water, carbohydrates, proteins, fiber, and fat, as well as essential amino acids, vitamins, and minerals. When garlic is cut, chopped, or crushed, the clove’s membrane is disrupted and S-allylcysteine sulfoxide (an odorless compound called alliin) is transformed enzymatically into alliin by alliinase (1). Alliin is responsible for the typical odor of garlic, but it is unstable and converts readily into mono-, di-, and trisulfides and other compounds such asajoene. Onions mainly contain S-propenylcysteine sulfoxide (1), but other sulfoxides, including S-propenylcysteine sulfoxide and S-methylcysteine sulfoxide (2). S-Propenylcysteine sulfoxide, positional isomer of alliin, is called larnacatory precursor, because it is transformed by alliinase into the larnacatory factor propanethial S-oxide. The larnacatory factor is highly reactive and hydrolyzes to propionaldehyde, sulfuric acid, and hydrogen sulfide; it is also the precursor of several sulfur derivatives. Organosulfur compounds present in Allium vegetables, which are either lipid or water soluble (Table 1), are considered responsible for the beneficial effects of these herbs. Garlic derivatives generally have a thioalyl moiety, whereas onion extracts contain a thiopropyl group with somewhat different chemical properties. The amounts of volatile compounds present in garlic bulbs are reported in Table 2.

Further transformation of organosulfur compounds can occur after interaction with free sulfhydryl groups, including those present in cysteine, glutathione, or proteins (4,5). Incubation of cysteine with allyl disulfide or diallylsulfide groups produces S-allylmercaptocysteine and alliinmercaptan, respectively (6). S-Allylmercaptocysteine is further transformed to alliinmercaptan following incubation with fresh blood. One study (7) in the isolated, perfused rat liver showed that alliin is first metabolized to diallyldisulfide, which is further reduced to allylmercaptan. Another study identified allylmercaptan and allylmethylelsulfide as metabolites of diallyldisulfide and diallylsulfide in primary rat hepatocytes (8). Urine from healthy individuals consuming garlic or onions contains N-acetyl-S-allylcysteine and N-acetyl-S-(2-carboxypropyl)-cysteine (9–11). Allylmercaptan and diallylsulfide have been found in human breath after ingestion of garlic (12,13).

Epidemiologic Studies

The association between consumption of Allium vegetables and risk for cancer has been assessed in several epidemiologic, mainly case-control, studies. One of the first indications of a role of Allium vegetables in the prevention of stomach cancer came from China. The 10-fold difference in the death rate from stomach cancer in two Chinese provinces was suggested to be attributable to garlic consumption, which was approximately 20 g/day in the low-risk area and <1 g/day in the high-risk area (14). This hypothesis was further supported by the results of an ecologic study in China (15), which reported that 82.3% of men and 74.7% of women in a low-risk area consumed garlic more than...
three times per week, whereas only 0.5% of the population in a high-risk area did so. Similar differences were found for the consumption of Welsh onions, onions, and Chinese chives.

Several case–control studies in Asia and Europe have been conducted to assess the effect of Allium vegetables on the risk of stomach cancer (Table 3 (16–27)). Most reported a decreased risk with increasing consumption. In one study (17) a higher risk for stomach cancer was found with increasing frequency of onion consumption, but the control group had a higher frequency of gastric diseases, including chronic or acute gastritis, gastric ulcer, and polyps. No association with onion consumption was found in two other studies (19,23). In a multicenter case–control study in areas of high and low risk for stomach cancer in Italy (20), use of garlic and onions as condiments decreased the risk of stomach cancer. When questions on the frequency of garlic consumption were added to a questionnaire given to a subgroup of subjects, an inverse association was observed between consumption of raw garlic and cancer risk, persons in the highest tertile of intake having only 40% of the risk of those in the lowest. The effects of different Allium vegetables have been evaluated separately in a few studies. You et al. (21) showed that patients with gastric cancer consumed approximately 3.5 kg less Allium vegetables per year than controls (15.5 vs. 19). Each Allium vegetable was associated with a decreased risk, which was most marked for scallions, garlic, and Chinese chives. Similar results were obtained when the usual diet 25–30 years before diagnosis (before the Cultural Revolution) was considered. In a population–based study, the age- and sex-adjusted odds ratio for stomach cancer decreased inversely with the frequency of consumption of garlic, onions, Welsh onions, and Chinese chives (26). This study also showed a decreased risk for esophageal cancer with a higher frequency of consumption of individual Allium vegetables (Table 4 (28,29,29)).

A cohort study in the Netherlands addressed the effect of daily use of onions, leeks, and garlic supplements for at least 15 years before baseline on the risk for stomach cancer (27) and for colorectal, breast, and lung cancers. Overall, cases were associated with lower consumption of onions and leeks, but slightly greater use of garlic supplements (9.2% vs. 8.8%). Onion consumption was significantly inversely correlated with the risk of stomach cancer, with a statistically significant trend for trend (Table 3). Slightly different results were obtained in stratified and multivariate analyses, but the trends remained statistically significant. Leek consumption was associated with a decreased risk only for persons in the highest category of consumption, but there was no clear decreasing trend. The relative risk associated with use of garlic supplements was slightly greater than 1.0. Similar results were obtained when cases occurring in the first year of follow-up were excluded from the analysis and when only subjects without a history of gastric disorders were considered. This study has the advantages of good completeness of follow-up and adjustment for factors, although no distinction was made between raw and cooked onions and leaks.

The chemopreventive effects of Allium vegetables against stomach and esophageal cancers may be related to their antibacterial properties. Inhibition of bacterial growth in the gastric cavity may result in less conversion of nitrate to nitrite in the stomach (14), a decreased probability of endogenous formation of carcinogenic N-nitroso compounds, and reduction in Helicobacter pylori infection specifically. In vitro, garlic oil and extracts of individual organosulfur compounds strongly inhibit the bacterial growth of H. pylori (30–33). In contrast, some studies in humans showed no correlation between seropositivity to H. pylori and the consumption of garlic (34) or use of garlic to treat H. pylori infection (35).

A clinical intervention trial is being conducted in China in which capsules containing steam-distilled garlic oil and aged garlic extract (in addition to amoxicillin and omeprazole or antioxidants) are given to determine whether they reduce the prevalence of dysplasia and other preneoplasmic lesions in the stomach (36). No results have yet been published.

Studies of the effects of Allium vegetables against colorectal cancer are summarized in Table 5 (17,37–46). Apart from the study of Tajima and Tominaga (17) discussed above, the case–control studies generally found decreased risks for colorectal cancer. The effect was particularly significant for consumption of cooked onions and leaks in Belgium (38), for a combination of garlic, onions, and pepper in Argentina (40), and for garlic in Switzerland (43). In a case–control study in Australia, Stähnmetz and Potter (41) reported a lower risk for both sexes, with a more pronounced decrease for women and for cancer of the proximal compared with the distal colon. Nevertheless, two of the three control studies reported decreased risks for cancer of the distal colon with higher consumption of garlic (44,45). The third control study showed no significant effect of consumption of onions, leaks, and garlic supplements (46).
An increased frequency of consumption of garlic and onions was associated with a decreased risk for breast cancer (Table 6 (47–50)) in case-control studies in Switzerland and France (48,49), but a case-control study in Greece (47) and the cohort study in the Netherlands showed no effect of Allium vegetables (50).

Studies of the association between consumption of Allium vegetables and risk for cancers at other sites are summarized in Table 7 (51–57). In case-control studies, significantly decreased risks with onion consumption for cancer of the lung in India (51) and of the brain in China (56) were reported. A significantly decreased risk for cancer of the larynx with garlic consumption was reported in China (53). A case-control study in England (55) reported a significant protective effect against prostate cancer when garlic was eaten as a food and as a food and supplement, but no effect was seen with onions. However, adjustment for social class reduced the association with garlic to nonsignificance. A moderate protection of endometrial cancer was also reported with Allium vegetable consumption (57).

Studies summarized above can suffer from some limitations, including use of hospital-based controls, low response rates among cases or controls, low rates of histologic confirmation of the tumors, use of recent diet as a reference, use of frequency instead of amount consumed, bias due to differential recall of dietary intake associated with awareness of disease, and absence of information on vegetable preparation (i.e., raw or cooked). These factors could explain some inconsistencies in Table 3. Epidemiologic studies of consumption of Allium vegetables and risk for stomach cancer.

| Country        | Cases/controls | Time of reference | Allium vegetable | OR* (p-value for trend) | Adjusted for confounding | Reference |
|----------------|----------------|-------------------|------------------|-------------------------|--------------------------|-----------|
| Case-control studies |                |                   |                  |                         |                          |           |
| Hawaii (Japanese) | 220/440 (hospital) | Current diet | Onions (frequency) | 0.48 Hawaiian Japanese 0.67 Japanese migrants 0.31 Migrant offspring | Sex | (16) |
| Japan | 93/186 (hospital) | 1–2 Years before onset | Onions (frequency) | 2.13 | Age, sex | (17) |
| Greece | 110/100 (hospital) | Before onset | Onions (frequency) | 0.68 (< 0.001) | — | (18) |
| China | 241/241 (hospital) | Before onset | Onions, chives (kg/year) | No significant effect | — | (19) |
| Italy | 1,016/1,159 (population) | 2 Years before interview | Onions, garlic as condiments (frequency) | 0.8 (0.04) | Age, sex, study area, social class, residence, migration, Quetelet index, family history of gastric cancer | (20) |
| China | 564/1,131 (population) | 6–8 Years before onset | Total Allium vegetables (kg/year) | 0.4 (< 0.01) | Age, sex, family income, intake of other Allium vegetables | (21) |
| Poland | 741/741 (hospital) | Before onset | Scallions (kg/year) | 0.8 (0.02) | — | (22) |
| Spain | 354/354 (hospital) | 1 Year before onset | Onions (high vs low) | 0.9 | Total calories, intake of salad, tomatoes, chard, spinach, borage, green beans, cruciferous vegetables | (23) |
| Belgium | 449/3,524 (population) | Before onset | Cooked onions (g/week) | 0.3 (< 0.0001) | Age, sex, province | (24) |
| Sweden | 338/669 (population) | 20 Years before interview | Cooked leeks (g/week) | 0.29 (< 0.0001) | Age, sex, socio-economic status | (25) |
| China | 153/234 (population) | Not specified | Garlic (frequency) | 0.89 | Age, sex, income, smoking, drinking, tea consumption, intake of leftover gruel, pickled vegetables, meat, fruit, tomatoes, eggs, snap beans | (26) |
| Cohort study | The Netherlands | 139/3,123 | Onions (n/day) | 0.50 (0.03) | Age, sex, education, smoking status, intake of alcohol, vitamin C, β-carotene, history of stomach disorders, family history of stomach cancer | (27) |

*Odds ratio: highest versus lowest consumption.
the results. Publication bias, with limited number of published data with no apparent protective effect, could also be operating and detracting from the evidence of an effect. However, studies assessing the role of Allium vegetables in cancer prevention have generally not been designed for this purpose, and it is therefore possible that finding no effect for Allium vegetables did not really affect the publication.

For calculation of odds ratios, the data were generally adjusted for age and sex and other variables, including socioeconomic status, anthropony, and family history of gastric disorders and cancer. Alcohol, smoking, and energy intake were also taken into account in some studies. However, consumption of other food items, including vegetables, was adjusted for in few studies (23, 26, 27, 43, 46, 50, 52). Such adjustment seems essential in studies of gastric cancer, because low consumption of green vegetables and fruits has been described as an important risk factor for this cancer. Epidemiologic studies summarized here are generally very consistent in reporting a protective effect of Allium vegetables in gastric cancer, and the adjustment for fruits and vegetables was made in studies showing either protection (26, 27) or lack of effect (23). It seems, therefore, that such adjustment is not the only factor explaining differences in results.

**Experimental Carcinogenesis**

The effects of Allium vegetables have been studied experimentally by testing individual organosulfur compounds or extracts and oils from garlic and onions (Table 8 (58–74)). The sulfur compounds were generally administered intragastrically before the carcinogen, at doses ranging between 0.01 and 0.2 mmol/rat or mouse, diluted in the diet (200–2,000 ppm) or percutaneously. Garlic was administered as a powder at 1–4% in the diet or as an extract at 400 mg/kg bw intragastrically.

Garlic contains compounds that inhibit the initiation step of carcinogenesis at a variety of sites in different animal species and with different initiators. Diallylsulfide (DAS) generally inhibited cancers of the forestomach, colon, esophagus, mammary gland, and lung (58, 60, 64, 65). Contradictory results were obtained with regard to the prevention of liver cancer (62, 69). Other allyl derivatives, including diallyl disulfide, allyl methyl disulfide, and allyl mercaptan (DADS, AMDS, and AM, respectively), decreased tumor formation in the forestomach and lung, but the related saturated propyl derivatives propyl methyl disulfide, propyl methyl trisulfide, diallyl sulfide, and diallyl trisulfide (PMDS, PMTS, DPTS, and DPT, respectively) did not (58, 59). Diallyl trisulfide (DATS) and allyl methyl disulfide (AMTS), which contains two allyl group, being more potent than AMTS, the analogue derivative with only one allyl group (58). This finding underlines the importance of the allyl group for cancer-preventive activity. These trisulfide derivatives, AMTS and DATS, were not effective against pulmonary adenoma formation, suggesting that the number of sulfur atoms in the molecule is also important, possibly determining the organ sites at which protection is achieved against carcinogenesis (58). DADS was also protective against cancers of the colon, mammary gland, and kidney (62, 63, 65, 67). S-allylcysteine (SAC) inhibited the incidence and frequency of 1,2-dimethylhydrazine (DMH)-induced colon tumors (61). Contradictory results were reported with SAC for N-methylnitrosourea (MNU)-induced mammary carcinogenesis (67, 68). These inconsistencies could be explained by differences in the doses of MNU and SAC used and the type of diet administered. Garlic powder in the diet inhibited mammary tumors (65–67), and garlic extract decreased the incidence of cervical carcinoma (70). DAS and garlic oil applied topically during the initiation phase of skin cancer reduced the number of tumors per mouse (72, 74). In addition, garlic extract and garlic and onion oil decreased the promotion step of skin carcinogenesis induced by 12-O-tetradecanoylphorbol 13-acetate (71, 73). The protection provided by garlic against carcinogenesis may be modulated by various dietary components, including selenium, vitamin A, and lipids (65, 75, 76).

The finding of lack of cancer-preventive effect of organosulfur compounds could have affected the publication of the study; however, the protective effect seems to be very consistent, and publication bias appears unlikely.

**Mechanisms of Cancer Prevention**

Several mechanisms have been proposed to explain the cancer-preventive effects of Allium vegetables and related organosulfur compounds. These include inhibition of mutagenesis, modulation of enzyme activities, inhibition of DNA adduct formation, free-radical scavenging, and effects on cell proliferation and tumor growth. Although there is evidence supporting these mechanisms for organosulfur compounds, they are still speculative, and further research is needed to support a causality between such properties and the cancer-preventive activity in experimental animals.

**Inhibition of mutagenesis.** Aqueous and methanolic garlic extracts inhibited the mutagenic activity of aflatoxin B1 in Salmonella typhimurium (77). Aqueous garlic extract also decreased the mutagenicity of 4-nitroquinoline-1-oxide in Escherichia coli (78) and the mutagenicity of γ-radiation, hydrogen peroxide, cumene, and t-butyldihydroperoxides in S. typhimurium (79). Onion juice protected S. typhimurium against cooked mutagens present in hamburgers (80).

**Modulation of enzyme activities.** Organosulfur compounds have been shown to modulate the activity of glutathione S-transferases (GST), a family of enzymes important in detoxification of carcinogens, and cytochromes P450 (CYP), a family of enzymes that activate many chemical carcinogens in experimental animals. Sparnins and co-workers (81) first showed that AMTS increased the activity of

---

**Table 4. Case-control studies of consumption of Allium vegetables and risk for esophageal cancer in China.**

| Cases/controls | Time of reference | Allium vegetable | OR* (p-value for trend) | Adjusted for | Reference |
|---------------|------------------|-----------------|------------------------|--------------|----------|
| 196/392 (hospital) | Before onset | Onions (kg/year) | 0.7 (0.33) | Alcohol, income, occupation, smoking | (28) |
| | | Garlic (kg/year) | 1.0 (0.24) | Age, education, birthplace, cigarette smoking, tea and alcohol drinking | (29) |
| 902/1,552 | 5 Years before interview | Allium vegetables (frequency) | M en 1.1 (0.69) | Age, sex, income, smoking, drinking, tea consumption, intake of leftover gruel, pickled vegetables, meat, fruits, tomatoes, eggs, snap beans | (26) |
| 153/234 (population) | Not specified | Garlic (frequency) | 0.30 | | |
| | | Onions (frequency) | 0.25 | | |
| | | Welsh onions (frequency) | 0.15 | | |
| | | Chinese chives (frequency) | 0.57 | | |

*Odds ratio: highest versus lowest consumption.
GST in the forestomach, small-bowel mucosa, liver, and lung of mice. Other allyl derivatives also increased GST activity in these tissues (58). Derivatives with a propyl instead of an allyl group were less active or inactive. The induction of GST paralleled the inhibition of benzo[a]pyrene-induced carcinogenesis in the forestomach, but not in the lung, suggesting that increased carcinogen detoxification is only one of the factors responsible for the cancer-preventive effects of organosulfur compounds. These results were partially confirmed by Sumiyoshi and Wargovich (61), who found a greater effect of thioallyl than thiopropyl derivatives in inducing hepatic and colonic GST in mice. In contrast, DAS did not increase GST activity in mouse liver (60) or in a culture of rat hepatocytes (69).

The activity of mammary and liver GST was increased by the addition of garlic powder to the diet of rats (66). The maximum activity of GST did not coincide with maximum inhibition of carcinogenesis, however, further indicating that increased GST activity does not account fully for the protection provided by garlic powder against carcinogenesis. Thus, the effects on enzymes that activate chemical carcinogens are not sufficient to explain the cancer-preventive activity. For example, an oral dose of DAS suppressed

---

**Table 5. Epidemiologic studies of consumption of Allium vegetables and risk for colorectal cancer.**

| Country     | Cases/controls | Time of reference | Allium vegetable | OR* (p-value for trend) | Adjusted for confounding                                      | Reference |
|-------------|----------------|-------------------|------------------|-------------------------|--------------------------------------------------------------|-----------|
| **Case-control studies** |                |                   |                  |                         |                                                              |           |
| Japan       | 588/1,176 (hospital) | Not specified     | Japones leeks (frequency) | Colorectum 0.78          | Age, sex, prefecture                                        | (37)      |
| Japan       | 93/186 (hospital)    | 1-2 Years before onset | Onions (frequency)   | Low rectum 0.65           |                                                              |           |
| Belgium     | Colon 453/2,851 Rectum 365/2,851 (population) | 1 Week before onset | Cooked onions (g/week) | Colorectum 0.29          |                                                              |           |
| China       | 336/336 (hospital) | Before onset       | Garlic (yes/no)     | Rectum, women 0.21        |                                                              | (39)      |
| Argentina   | 220/438 (population) | 1 Year before interview | Garlic, onions, pepper (frequency) | Rectum, women 0.004     |                                                              | (40)      |
| **Cohort studies** |                |                   |                  |                         |                                                              |           |
| United States | 212/35,004 Last year before interview | Garlic (frequency) | Colon | Men 0.86 Women 0.23 | Age, energy intake                                          | (44)      |
| United States | 205/47,949 Last year before interview | Garlic (frequency) | Colon | Men 0.77 Women 0.38 | Age, energy intake                                          | (45)      |
| The Netherlands | 443/3,123 Last year before interview | Onions (g/day) | Low rectum 0.65 | Colon 0.68 Proximal colon 1 | Age, energy intake                                          | (46)      |

*Odds ratio: highest versus lowest consumption.
esophageal carcinogenesis induced by N-nitrosomethylbenzylamine in rats and significantly reduced the microsomal conversion of this nitrosamine in liver but not in esophagus (64). In addition, the prevention of benzo[a]pyrene-induced forestomach cancer in mice by organosulfur compounds is not attributable to a reduction in the activity of CYP1A1 (82).

DADS in the diet increased not only the activity of GST but also that of other detoxifying enzymes, including reduced nicotinamide adenine dinucleotide phosphate (NAD(P)H)-dependent quinone oxidoreductase, which is involved in detoxification of activated quinone metabolites of benzo[a]pyrene, and of uridine diphosphate (UDP)-glucuronosyl transferase in rat tissues (63,83).

DAS acted as a competitive inhibitor of N-dimethylnitrosamine demethylase activity (84). It also decreased the activity of CYP2E1 in a time- and dose-dependent manner and induced the activities of CYP2B1 and pentoxy- and ethoxyresorufin dealkylases in hepatic microsomes (85). An increase in CYP2B1 mRNA was also observed. Treatment with the DAS metabolites diallyl sulfide (DASO) and diallylsulfone (DASO2) had similar effects on rat hepatic monoxygenase activities (85,86). Reicks and Crankshaw (87) reported that DAS, DADS, and AMS decreased p-nitrophenoxy hydroxylation activity and CYP2E1 protein concentration in rat liver. When the diet of rats was supplemented with DAS or DADS (88), DADS increased the activities of several monoxygenases and transferases in intestine and liver; the protein levels of epoxide hydrolase and CYP2B1/2 were also increased. DADS also decreased CYP2E1 level in liver. The effects of DAS were similar to those of DADS in liver, but only epoxide hydrolase activity and CYP2B1/2 protein levels were increased in the intestine.

In a study of the effect of garlic oil, DAS, and DADS on the activities of several metabolizing enzymes in the liver of rats fed high-fat diets (89), GST activity was increased by all treatments. Garlic oil induced the expression of the placental form of GST and CYP2B1 and decreased the expression of CYP2E1. DAS and DADS also modulated these enzymes, but DAS increased mainly CYP2B1, whereas DADS increased mainly GST activity; similar effects were observed on CYP2E1 expression.

DAS and its oxidation derivatives DASO and DASO2 are conjugated with glutathione in rats (90). To our knowledge, no study has investigated the effects of possible GST polymorphisms in the detoxication of these Allium vegetable-derived compounds, although this could provide some explanations of differential effects in humans.

Modulation of the activity of arylamine N-acetyltransferase, a polymorphic enzyme that deactivates arylamines and activates some heterocyclic dietary amines, was addressed in a few studies. The slow and fast acetylator phenotypes have been associated with increased risk for cancers of the bladder and colon, respectively. DAS and DADS decreased the activity of this enzyme in strains of H. pylori from peptic ulcer patients (31) and inhibited its activity in a human colon tumor cell line (91) and in human bladder tumor cells (92) in a dose-dependent manner.

**Inhibition of DNA adduct formation.** DNA adducts are believed to be an initial step in carcinogenesis by chemicals. In rat mammary gland, garlic powder decreased the occurrence of 7,12-dimethylbenz[a]anthracene (DMBA)–DNA adducts in vivo and the amounts of total and individual adducts correlated positively with mammary tumor incidence (66). Garlic powder, garlic water extract, a deodorized garlic powder, a garlic powder with a high sulfur content, and SAC were also effective against mammary DMBA–DNA binding (93).

DNA adducts induced by incubation of human bladder tumor cells with 2-aminofluorene were inhibited by DAS and DADS (92). In contrast, a water extract of raw garlic and SAC, but not DAS, significantly inhibited benzo[a]pyrene-DNA adduct formation in simulated human peripheral blood lymphocytes in vitro (94).

N-Nitroso compounds, a class of potential human carcinogens that can be synthesized in humans from precursors present in the diet, are metabolized to alkylating agents that can bind to DNA. Shenoy and Choughuley (95) showed that onion and garlic juices inhibit the nitrosation reactions in vitro in a dose-dependent manner. The occurrence of 7-methoxydeoxyguanosine (7-MdG) and O6-methyldeoxyguanosine (O6-MdG) was decreased in rat liver when garlic powder was added to a diet containing aminopurine and sodium nitrite (96). Garlic powder also decreased DNA methylation in the livers of rats treated with N-nitrosodimethylamine and in mammary tissue of rats treated with N-methylnitrosourea. Garlic, SAC, and DADS also decreased the formation of 7-MdG and O6-MdG induced by N-methylnitrosourea in mammary DNA; this decrease correlated with the inhibition of mammary tumors by these compounds (67).

**Table 6.** Epidemiologic studies of consumption of *Allium* vegetables and risk for breast cancer.

| Country      | Cases/controls | Time of reference | Allium vegetable         | OR² (p-value for trend) | Adjusted for confounding | Reference |
|--------------|----------------|-------------------|--------------------------|------------------------|--------------------------|----------|
| Case-control studies |                |                   |                          |                        |                          |          |
| Greece       | 120/120 (hospital) | Before onset       | Onions, leeks (frequency) | No significant effect  | Age, education           | (47)     |
| Switzerland  | 107/318 (hospital) | Before onset       | Garlic (frequency)        | 0.6 (0.05)             | Age                      | (48)     |
| France       | 345/345 (selected population) | Before interview | Garlic, onions (frequency) | 0.3 (<0.0001)         | Total caloric intake, parity, weight, corporeal surface | (49)     |
| Cohort study |                |                   |                          |                        |                          |          |
| The Netherlands | 469/1,713     | Last year before interview | Onions (n/day) | 0.95 (0.65) | Age, parity, age at menarche, age at first birth, age at menopause, artificially induced menopause, oral contraceptive use, alcohol consumption, education, Quetelet index, smoking status, dietary intake of vitamin C and β-carotene, history of benign breast diseases, breast cancer in mother and sister | (50)     |

*Odds ratio: highest versus lowest consumption.*
Free-radical scavenging. Free radicals have been related to several age-related diseases, including cancer (97). Reduced glutathione (GSH) is not only a cofactor for GST but also serves as a reductant for glutathione peroxidase (GPX), an enzyme involved in natural protection by free radicals, in addition to superoxide dismutase and catalase. Garlic and onion oils stimulated the activity of GPX and inhibited the decreased ratio of reduced to oxidized glutathione produced by 12-O-tetradecanoylphorbol-13-acetate in epidermal cells (98). GPX activity was also increased in animal tissues with DAS (99), DADS and garlic oil (89). DAS and DADS also increased the activity of glutathione reductase, and garlic oil increased the activity of superoxide dismutase (89). In contrast, DAS and garlic homogenates decreased catalase in the livers of rats and mice (100). S-Allylmercaptosysteine (SAMC) and SAC increased the synthesis of GSH in human prostate cancer cells (101).

Aged garlic extract, SAC, and SAMC exhibited radical scavenging activity (102). DAS, DADS, and AMS showed selective actions on different markers in tests for their ability to react with carbon tetrachloride-derived free radicals (103). DADS also inhibited carbon tetrachloride-induced lipid peroxidation. The antioxidant properties of Allium vegetables might therefore result from the contributions of various sulfur components at different steps of the process.

Effects on cell proliferation and tumor growth. Inhibition of tumor cell proliferation by organosulfur compounds has been reported in several studies using different cell cultures, including canine mammary tumor cells (104), human colon, lung, and skin tumor cell lines (105,106), human neuroblastoma cells (107), human and murine melanoma cells (108), and human prostatic carcinoma cells (109).

Contradictory results have been obtained with regard to modulation of the proliferative activity of non-neoplastic cell lines by organosulfur compounds, with some studies showing inhibition (108,109) and others no effect (106).

Garlic and onion oils caused a marked suppression of proliferation of human promyelocytic leukemia cells (110). Garlic powder and an alliin-enriched garlic extract inhibited the growth of a human lymphatic leukemia cell line in a dose-dependent manner, but inhibited the growth of human hepatoma and human colorectal carcinoma cells only when applied as a mixture. This finding indicates that the antiproliferative effect of garlic is due to breakdown products of alliin catalyzed by the alliinase enzyme system present in garlic powder (111).

Polyamines, mainly spermine, play an important role in cell division and differentiation. SAMC, but not SAC, has been shown to alter polyamine concentrations in human prostate carcinoma cells, increasing that of spermidine and decreasing those of putrescine and spermine (101). Ornithine decarboxylase,
a rate-limiting enzyme involved in the synthesis of polyamines, is also reduced by DAS (98,112,113), although there is evidence of an increase in the livers of rats not treated with initiators (114).

The antiproliferative effect of organosulfur compounds appears to be related to the induction of apoptosis. Exposure to DADS and DATS caused cells to undergo apoptosis, as determined by morphologic changes and/or DNA fragmentation (105,106). A positive correlation was found between DADS-induced DNA fragmentation and increased intracellular free-calcium concentration, which may activate calcium-dependent endonucleases leading to apoptosis. A recent study (115) showed that DAS, DADS, and garlic extract increase the number of non-small-cell lung cancer cells in the apoptotic state. This increase followed the induction of p53 protein by DADS or the increase of the expression of Bax and decrease of the expression of Bcl-2 by DADS, and garlic extract. Ajoene induced apoptosis in human leukemic cells but not in peripheral mononuclear blood cells from healthy donors (116). The cell cycle was also affected by DADS, which decreased the percentage of human colon tumor cells in the G1 and S phases and concomitantly increased the percentage of those in the G2/M phase (117). These effects depend on the dose of DADS and the length of incubation. The ability of DADS to inhibit cell proliferation was related to induction of G2/M phase arrest and to inhibition of p34<sup>cdc2</sup> kinase activity, which modulates the progression of cells from G2 into the M phase of the cell cycle. The suppression of the p34<sup>cdc2</sup> kinase activity by DADS resulted not from a direct interaction with the protein but from modulation of the factors involved in the formation and conversion of the enzyme to its active form (118). DADS also significantly inhibited the growth of H-<i>r</i>as oncogene-transformed tumors implanted in nude mice by suppressing the association of p21<sup>H-ras</sup> with the cell membrane (119).

**Conclusions**

Overall, evidence shows that Allium vegetables, mainly garlic and related organoallyl sulfur compounds, have cancer-preventive effects. In the 37 case-control or cohort studies for cancer at any site reported here, 28 showed some protective effect of Allium vegetables. The evidence is particularly strong for stomach cancer (9 out of 12 studies) and colon cancer (9 out of 11 studies), while there is still insufficient evidence for an effect on breast, lung, and other cancers. A recent meta-analysis also showed that a high intake of garlic may be associated with decreased risks for stomach and colorectal cancer (120).

However, the epidemiologic data do have some limitations, which decrease the strength of the evidence currently available. For example, consumption is often reported as frequency instead of amount consumed, and the consumption categories differ widely among studies. In addition, the meta-analysis (120) indicated that the apparent protective effect found between Allium vegetable consumption and cancers of the stomach and colon may have been overestimated, suggesting a possible publication bias. Lack of adjustment in the statistical analyses also limits the strength of the conclusion. For example, the data for stomach cancer were generally not adjusted for fruit and vegetable consumption, which are known to be protective and could therefore be a confounder in the analysis. Clinical trials are not currently available, but they could be useful for assessing the ability of garlic and other Allium vegetables to prevent cancer or pre-neoplastic lesions. There are difficulties in standardizing the real intake of Allium vegetables, and in estimating the composition in organosulfur compounds and other chemicals. In addition, these trials cannot use cancer as the end point and should therefore rely on surrogate intermediate biomarkers (121). Such end points are not fully validated, and further research is needed to develop and validate suitable biomarkers.

Studies in experimental animals indicate that the benefits of Allium vegetables are not limited to one species, tissue, or carcinogen. Organosulfur compounds can hinder activation of a carcinogen from its precursor, increase its metabolic detoxification, or

---

**Table 8. Effects of Allium vegetable components on carcinogenesis in experimental animals.**

| Organ            | Chemical component | Animal species, doses | Carcinogen     | Effect on carcinogenesis | Reference |
|------------------|--------------------|-----------------------|----------------|--------------------------|-----------|
| Forestomach      | AMDS, AMTS, DAS, DATS PMDS, PMTS, DPS, DPTS AMDS, DADS, AM | Mouse, 0.02 mmol, po | BaP            | Inhibition               | (58)      |
|                  |                    | Mouse, 0.01-0.02 mmol, po | NDEA           | No effect                | (59)      |
| Colon            | DAS                | Mose, 200 mg/kg bw, po | DMH            | Inhibition               | (60)      |
|                  | SAC                | Mose, 50-100 mg/kg bw, po | DMH            | Inhibition               | (61)      |
|                  | DAS, DADS          | Rat, 50-200 mg/kg bw, po | Combination   | Inhibition (DADS)        | (62)      |
|                  | DADS               | Rat, 200 ppm in diet   | AOM            | Inhibition               | (63)      |
| Esophagus        | DAS                | Rat, 200 mg/kg bw, po  | NMBA           | Inhibition               | (64)      |
| Mammary gland    | DAS, DADS, AMS    | Rat, 1.8 mmol/kg bw, po | DM BA          | Inhibition               | (65)      |
|                  | Garlic powder      | 20 g/kg diet           |                |                          |           |
|                  | Garlic powder      | Rat, 1-4% in diet      |                |                          |           |
|                  | SAC, DADS          | Rat, 57 mmol/kg diet   | M NU           | Inhibition               | (66)      |
|                  | Garlic powder      | 20 g/kg diet           |                |                          |           |
|                  | SAC                | Rat, 666 and 2,000 ppm in diet | M NU | No effect                | (68)      |
| Lung             | AMDS, DAS, AMTS, DATS PMDS, PMTS, DPT | Mose, 0.02 mmol, po | BaP            | Inhibition               | (58)      |
|                  | DADS, AMS, AMTS    | Mose, 0.01-0.02 mmol, po | NDEA           | No effect                | (59)      |
|                  | DADS, DADS, AM     | 50-100 mg/kg bw, po    | DMH            | Inhibition               | (69)      |
| Liver            | DAS                | 50-200 mg/kg bw, po    | Combination   | Increase (DAS)           | (62)      |
|                  | DADS, DADS         | 50-200 mg/kg bw, po    | Combination   | Inhibition (DADS)        | (62)      |
| Kidney           | DAS, DADS          | 50-200 mg/kg bw, po    | M CA           | Inhibition               | (70)      |
| Uterine cervix   | Garlic extract     | Mose, 400 mg/kg bw, po | DM BA-TPA      | Inhibition (mainly onion oil) | (72)      |
| Skin             | Garlic oil, onion oil | Mose, 10 μg-10 mg, pc | DM BA          | Inhibition               | (71)      |
|                  | Garlic extract     | Mose, 5 mg dry weight, pc | DM BA-TPA     | Inhibition               | (73)      |
|                  | DAS                | Mose, 250 μg, pc       | DM BA, BaP    | Inhibition               | (74)      |

Abbreviations: AOM, azoxymethane; BaP, benz(a)pyrene; DM BA, 7,12-dimethylbenz(a)anthracene; DM H, 1,2-dimethylhydrazine; M CA, 3-methylcholanthrene; M NU, N-methylnitrosourea; NDEA, N-nitrosodimethylamine; NMBA, N-nitrosomethylbenzylamine; po, per os; TPA, 12-O-tetradecanoylphorbol-13-ace-tate.
prevent its reaction with vulnerable target cells. Additional mechanisms include a delay or a reversion of the expression of malignant

necrosis by antiproliferative activity in tumor cells and modification of signal transduction mechanisms. These speculative mechanisms in animal models should be verified in human studies to establish a causative link between some molecular properties and the cancer-preventive activity.

Extrapolation of the doses of pure chemi-

cals that are effective in animals to their equivalent

definitions in terms of Allium vegetables leads to unrealistic estimates of the amounts that would have to be consumed by humans to benefit from the antitumor effects of these substances. For example, because the dose of DAS that is effective in animal's ranges from 50 to 400 mg/kg bw, a person weighing 70 kg would have to consume 3.5–25 g of DAS per day. T he dose range for DAS in the isolated perfused rat liver ranges from 0.03 to 0.1 mg/g; thus, 40–100 g of garlic would have to be consumed per day, corresponding to 10–100 garlic cloves per day. Epidemiologic studies have found a protective effect of consumption of much lower doses, the mean intake being 18.3 g/week (120).

Little is known about the stability of organosulfur compounds during cooking or about the metabolism, pharmacokinetics, and toxicity of the active compounds in humans. All these aspects require further attention if the use of garlic and other Allium vegetables are to be recommended for cancer prevention.

REFERENCES AND NOTES

1. Block E. The chemistry of garlic and onions. Sci Am 232:94–99 (1985).

2. Vitanen AL, Mikkikka EJ. The isolation of S-methyl-L-cysteine sulfoxide and S-propyl-L-cysteine sulfoxide from onion (Allium cepa) and the antibiotic activity of crucified onion. Acta Chem Scand 13:1898–1900 (1976).

3. Yu TH, Wu CM, Liu YC. Volatile compounds from garlic. J Agric Food Chem 37:725–730 (1989).

4. Wiesbarger AS, Pensky J. Tumor inhibition by a sulfhydryl-blocking agent related to an active principle of garlic (Allium sativum). Cancer Res 18:1031–1038 (1958).

5. Gilbert HF. Molecular and cellular aspects of thiolsulfuride exchange. Adv Enzymol Relat Areas Mol Biol 63:69–172 (1990).

6. Lawson LD, Wang Z. Pre-hepatic fate of the organosulfur compounds derived from garlic (Allium sativum). Plant Med 59:688–689 (1993).

7. Egen-Schwudt C, Eckard R, Kemper FH. Metabolism of garlic constituents in the isolated perfused rat liver. Plant Med 66:301–305 (1992).

8. Sheen LY, Wu CC, Li CK, Tsai SJ. Metabolites of diallyl disulfide and diallyl sulfide in primary rat hepatocytes. Food Chem Toxicol 37:1139–1148 (1999).

9. Jander J, Stippler G. Unusual conjugates in biological profiles originating from consumption of onions and garlic. J Chromatogr 421:1–8 (1987).

10. de Rooy BM, Boogaard P, Rijksen DA, Commandeur JN, Vermeulen NP. Aliphatic mercapturic acid as urinary biomarker of human exposure to allyl chloride. Occup Environ Med 45:633–636 (1998).

11. Laakso I, Seppanen-Laasko T, Hiltunen R, Muller B, Jansen H, Knobloch B. Volatile garlic oil components: garlic odors and garlic-like odor volatilized analyzable by headspace gas chromatography-mass spectrometry. Planta Med 55:257–261 (1989).

12. Minami T, Boku T, Inada K, Morita M, Okazaki Y. Odor components of fried garlic, garlic odors extracted by headspace gas chromatography-mass spectrometry. Planta Med 55:257–261 (1989).

13. Me I, Wang MC, Xu HK, Pan XY, Gao CY, Han N, Fu MY. Garlic and gastric cancer—the effect of garlic on nitrite in gastric juice. Acta Gastroenterol Belg 55:133–136 (1992).

14. Takeda T, Gao CM, Ding H, Liu TK, Li MS, Tajima K. Comparative study of lifestyles of residents in high and low risk areas for gastric cancer in Jiangsu Province, China; with special reference to Allium vegetables. J Epidemiol 9:297–301 (1988).

15. Haenszel W, Kurihara M, Segi M, Lee RK. Stomach cancer among Japanese in Hawaii. J Natl Cancer Inst 49:969–980 (1972).

16. Tajima K, Tommaga S. Dietary habits and gut- and intestinal- stem cancers: a comparative case-control study of stomach and large intestinal cancers in Nagoya, Japan. Jpn J Cancer Res 76:705–716 (1985).

17. Trichopoulou D, Ouranos G, Day NE, Tzonou A, Manousos O, Papadimitriou C, Trichopoulos A. Diet and cancer of the stomach: a case-control study in Greece. Int J Cancer 36:291–297 (1988).

18. Hu JF, Zhang EQ, Wang QG, Liu SD, Liu YW, Wu YP, Cheng YT. Diet and cancer of the stomach: a case-control study in China. Int J Cancer 41:331–335 (1988).

19. Bucki P, Dall DC, Amadori D, Avellini C, Bocci V, Cavallini G, Cocco P, Giaid A, et al. A multicenter case-control study of gastric cancer and diet in Italy. Int J Cancer 44:611–616 (1989).

20. You WC, Blot WJ, Chang YS, Ershow A, Yang ZT, An Q, Henderson BE, Franceschi S. Dietary substances. For example, because the dose of DAS that is effective in animals is range 0.03 to 0.1 mg/g; thus, 40–100 g of garlic would have to be consumed per day, corresponding to 10–100 garlic cloves per day. Epidemiologic studies have found a protective effect of consumption of much lower doses, the mean intake being 18.3 g/week (120).

Little is known about the stability of organosulfur compounds during cooking or about the metabolism, pharmacokinetics, and toxicity of the active compounds in humans. All these aspects require further attention if the use of garlic and other Allium vegetables are to be recommended for cancer prevention.
trol study of dietary factors and endometrial cancer in China. Reisheit EG, People’s Republic of China. Am J Epidemiol 137:155–165 (1993).

58. Spannins VL, Barany G, Wattenberg LW. Effects of organosulfur compounds from garlic and onions on benzo[a]pyrene-induced neoplasia and glutathione S-transferase activity in the mouse. Carcinogenesis 9:131–134 (1988).

59. Wattenberg LW, Spannins VL, Barany G. Inhibition of N-nitrosodimethylamine carcinogenesis in mice by naturally occurring organosulfur compounds and monoterpenes. Cancer Res 49:2689–2692 (1989).

60. Wargovich MJ. Diallyl sulfide, a flavor component of garlic, inhibits hepatic drug-metabolizing and antioxidant enzyme activities in rats. Cancer Res 50:5084–5087 (1990).

61. Takahashi S, Hakoi K, Yada H, Hirose M, Ito N, Fukushima S. Enhancing effects of diallyl sulfide on hepatocarcinogenesis and inhibitory actions of the related diallyl disulfide on colon and renal carcinogenesis in rats. Carcinogenesis 13:1513–1518 (1992).

62. Reddy BS, Rao CV, Rivenson A, Kellogg C. Chemoprevention of colon carcinogenesis by organosulfur compounds. Cancer Res 53:1349–1353 (1993).

63. Wargovich MJ, Woods C, Eng VW, Stephens LC, Gray K. Chemoprevention of N-nitrosobenzylamine-induced esophageal cancer in rats by the naturally occurring diallyl sulfide fraction of garlic. Cancer Res 48:687–689 (1988).

64. Ip C, Lisk D, Stoewsand GS. Mammary cancer prevention by regular garlic and selenium-enriched garlic. Nutr Cancer 17:279–286 (1992).

65. Liu J, Lin ML, Mliner A. Inhibition of 7,12-di/methylbenz[a]anthracene-induced mammary tumors and DNA adducts by garlic powder. Carcinogenesis 13:1847–1851 (1992).

66. Liu J, Rushmore TH, Goldberg T. Inhibition of hepatic carcinogenic responses to 12,12-di/dimethylbenz[a]anthracene by diallyl sulfide, a component of garlic. Carcinogenesis 8:1155–1157 (1987).

67. Hussan SP, Jannu LN, Rao AR. Chemopreventive action of garlic on methylcholanthrene-induced carcinogenesis in the uterine cervix of mice. Cancer Lett 102:199–204 (1996).

68. Cohen LA, Zhao Z, Pittman B, Lube R, S-allicyglycine, a gastric carcinogen, fails to inhibit N-methylnitrosourea-induced rat mammary tumorigenesis. Nutr Cancer 35:86–93 (1999).

69. Hayes MA, Rushmore TH. Goldberg T. Inhibition of hepatic carcinogenic responses to 12,12-di/methylbenz[a]anthracene by diallyl sulfide, a component of garlic. Carcinogenesis 8:1155–1157 (1987).

70. Munday R, Munday CM. Low doses of diallyl disulfide, a component derived from garlic, increase tissue activities of quinone reductase and glutathione transferase in the gas trointestinal tract of the rat. Cancer Res 43:24–48 (1989).

71. Braddy F, Lü DC, Ishizaki Y, Yang CS. Effect of diallyl sulfide on rat liver microsomal nitrosamine metabolism and other monooxygenase activities. Cancer Res 48:3991–3994 (1988).

72. Braddy F, Wang MH, Hong JY, Xiao F, Li Y, Lee JS, NING SM, Lee M, Fukuto M, Gapa C. Modulation of rat hepatic microsomal monooxygenase enzymes and cytotoxicity by diallyl sulfide. Toxicol Appl Pharm 108:342–354 (1991).

73. Pan J, Hong JY, Li DL, Schuetz EJ, Guzelian PS, Wang H, Yang CS. Regulation of cytochrome P450 2B1/2B2 genes by diallyl sulfone, disulfiram, and other organosulfur compounds in rats. Biochem Pharmacol 45:2232–2239 (1993).

74. Reicks MM, Crankshaw DL. Modulation of rat hepatic cytochrome P-450 activity by garlic organosulfur compounds. J Nutr 123:327–330 (1993).

75. Haber D, Siess MH, Canivenc-Lavier MC, Le Bon AM, Suzuki Y. Differential effects of dietary diallyl sulfide and diallyl disulfide on rat intestinal and hepatic drug-metabolizing enzymes. J Toxicol Environ Health 44:423–434 (1995).

76. Sheen LY, Chen HW, Kung YL, Liu CT, Li CK. Effects of garlic oil and its organosulfur compounds on the activities of hepatic drug-metabolizing and antioxidant enzymes in rats fed high- and low-fat diets. Nutr Cancer 35:160–166 (2001).

77. jin L, Baillie TA. Metabolism of the chemoprotective agent diallyl disulfide to glutathione conjugates in rat. Chem Res Toxicol 10:318–327 (1997).

78. Chen GW, Chung J, Hsieh CL, Lin J. Effects of the garlic components diallyl sulfide and diallyl disulfide on the expression of Bcl-2, Bax, and p53 in non small cell lung cancer cell lines. Lung Tumor Cells. Nutr Cancer 49:307–307 (1999).

79. Lin JT, Wargovich MJ. Effect of diallyl sulfide on N-nitrosonium intermediate and glutathione detoxification ability in the glandular stomach mucosa of the Wistar rat. Cancer Lett 47:153–159 (1989).

80. Siegers CP, Steffen B, Robke A, Pertz R. The effects of garlic preparations against human tumor cell proliferation. Phytomedicine 6:7–11 (1999).

81. Baer AR, Wargovich MJ. Role of ornithine decarboxylase in diallyl sulfide-induced inhibition of colon cancer cell proliferation. Cancer Lett 53:402–407 (1999).

82. Knowles LM, Mliner A. Depressed p38αβδ kinase activity and G2/M phase arrest induced by diallyl sulfide in HCT-15 cells. Cancer Nutr 30:169–174 (2004).

83. Knowles LM, Mliner A. Diallyl sulfide inhibits p38αβδ kinase activity through changes in complex formation and phosphorylation. Carcinogenesis 22:1139–1140 (2001).

84. Singh SV, Mohan RK, Agarwal R, Benson PJ, Xu Y, Ruddy M, Xia H, Katoh A, Srivastava SK, Mukhtar H, et al. Novel anti-carcinogenic activity of an organosulfide from garlic: inhibition of H-RAS oncogene transformed tumor growth in vivo by diallyl sulfide is associated with activation of p38αβδ and decreased levels of oxidized reduced glutathione. Biochem Biophys Res Commun 225:660–665 (1996).

85. Fleischauer AT, Cole P, Arab L. Garlic consumption and cancer prevention: meta-analyses of colorectal and stomach cancer. Am J Clin Nutr 62:5–82 (2000).

86. Miller AB, Bartsch H, Bottella P, Dragstedt L, Vainio H, edits. Biomarkers in Cancer Prevention. IARC Sci Publ 154:1–214 (2001).

902

Reviews • Bianchini and Vainio

September 2001 • Environmental Health Perspectives