Introduction

The contributions of environmental factors and diet in the development of cancer are highly controversial. In 1977, Sir Richard Doll stated, "Now one can hardly pick up a newspaper without reading that 80 or 90% of all cancers are environmental in origin and due to either industrial pollution, medical treatment, or an imprudent diet, depending on the policy of the paper or the idiosyncrasies of the speakers at the latest international conference," (Doll, 1977). Although there is some controversy regarding the relative contributions of naturally-occurring and endogenous carcinogens vs. exposure to trace levels of industrial compounds in the diet, there is no controversy regarding the important role of diet and various micronutrients in the prevention of cancer (Ames, 1998; Ames et al., 1995; Bertram and Frank, 1993.). Ames and coworkers (1998) have reviewed the role of dietary factors that are antitumorigenic and these include fruits and vegetables, fiber, folic acid, various antioxidants, vitamins B1, B6, C, and E, and trace metals such as iron, zinc, and selenium.

Development of cancer is a multi-step process that can be arbitrarily subdivided into initiation, promotion and progression steps that are required in transforming a normal cell into a neoplastic or tumor cell (Bertram and Frank, 1993). Naturally occurring anticarcinogenic compounds can play an important role in cancer prevention by inhibiting one or more of the important steps in tumor cell development. There is extensive ongoing research on identification of the more active anticarcinogenic compounds in fruits and vegetables and determining their mechanism of chemoprevention. Several phytochemicals induce phase II drug-metabolizing enzymes and probably act by metabolic detoxication of carcinogens, thereby inhibiting the initiation step in chemical carcinogenesis (Bertram and Frank, 1993). Sulforaphane [1-isothiocyanato-(4R)-(methyl-sulfinyl)butane] is a natural product that occurs in cruciferous vegetables such as broccoli, Brussels sprouts, and cauliflower, and this compound, along with other natural and synthetic isothiocyanates, inhibit development of multiple cancers in laboratory animal models (Nestle, 1997). Sulforaphane and other isothiocyanates are inducers of glutathione S-transferases and other phase II drug metabolizing enzymes, which play an important role in detoxication of potentially genotoxic radical or electrophilic chemicals by forming relatively non-toxic metabolite conjugates (Fahey et al., 1997; Nestle, 1997).

This symposium discussed the following four topics associated with anticarcinogenic phytochemicals: (a) the antiestrogenic and antitumorigenic activity of diindolylmethane; (b) the chemopreventive action of organosulfur compounds in alliums; (c) the mechanism of action and chemopreventive activities of the isoflavonoid genistein; and (d) polyphenolic compounds in green tea (Fig. 1). These structurally diverse chemicals inhibit development and/or growth of multiple tumors through diverse mechanisms and demonstrate, at the molecular level, the chemopreventive action of naturally occurring dietary chemicals.

Antiestrogenic and Antitumorigenic Activities of Diindolylmethane (S. Safe)

Background

Glucobrassicin (3-indolylmethyl glucosinolate) is a phytochemical conjugate of indole-3-carbinol (I3C) that has been identified in several plant species (Preobrazhenskaya et al., 1993) and occurs in relatively high concentrations in cruciferous vegetables such as cabbage (0.1 to 1.9 mmol/kg), cauliflower (0.1 to 1.6 mmol/kg), and Brussels sprouts (0.5 to 3.2 mmol/kg). High dietary levels of fruits and vegetables have been associated with cancer prevention in humans and the...
chemoprotective effects of cruciferous vegetables have been demonstrated in laboratory animal studies (Wattenberg and Loub, 1978). I3C inhibits formation and/or growth of tumors at multiple sites and several studies show that both Brussels sprouts and I3C inhibit mammary-tumor formation and progression in rodent models (Bradlow et al., 1991; Grubbs et al., 1997). The biochemical and anticarcinogenic activities of I3C have been extensively investigated (reviewed in Safe et al., 1996). Glucobrassin is readily hydrolyzed to give I3C; however, in the highly acidic environment of the gut, I3C is converted into multiple condensation products including 3,3′-diindolylmethane (DIM) and indolo[3,2-b]carbazole (ICZ) (Bjeldanes et al., 1991) and, therefore, many of the responses associated with exposure to I3C may be due to one or more of the acid-derived compounds. I3C and related compounds induce multiple activities in vivo and in various cell lines, including the induction of multiple phase 1 (CYP1A1, CYP1A2, CYP2B1, CYP3A1, epoxide hydrolase, NAD(P)H quinone oxidoreductase) and phase 2 (glutathione S-transferase and glucuronyltransferase) drug-metabolizing enzymes. Moreover, the overall design of many studies on inhibition of carcinogen-induced mammary cancer by I3C/Brussels sprouts are consistent with altered carcinogen metabolism since there is overlap in administration of the carcinogen and I3C.

**DIM as an AhR-Based Antiestrogen**

Previous studies have shown that I3C and related compounds competitively bind the aryl hydrocarbon receptor (AhR) where the order of receptor binding affinity was ICZ > DIM >> I3C, and ICZ was only 30–50 times less potent than the high affinity ligand 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) (Bjeldanes et al., 1991; Jellinck et al., 1993). Ongoing research in this laboratory has focused on AhR action, with specific emphasis on the mechanism of AhR-mediated antiestrogenic activity and development of new AhR-based drugs for treatment of breast cancer (Safe, 1995). TCDD is a toxic AhR agonist that inhibits multiple 17β-estradiol (E2)-induced responses in the rodent uterus and human breast-cancer cells in culture. Moreover, TCDD inhibits mammary tumor formation and growth in female rats and tumor growth in athymic mice bearing MCF-7 breast cancer-cell xenografts. Previous studies in this laboratory have identified alternate-substituted (1,3,6,8- and 2,4,6,8-)alkyl polychlorinated dibenzofurans (PCDFs) as relatively non-toxic AhR-based antiestrogens that also inhibit growth of carcinogen-induced mammary tumors in female Sprague-Dawley rats (McDougal et al., 1997). Alkyl PCDFs are selective AhR modulators (SAhRMs) and represent a class of drugs that target the AhR.

Initial competitive AhR binding studies showed that DIM bound to rat cytosolic AhR with an affinity similar to that described for TCDD (Chen et al., 1998). DIM also transformed the rat cytosolic AhR to form a specifically bound DNA-protein complex with [32P]-labeled dioxin responsive element (DRE) in a gel mobility-shift assay. Photoinduced crosslinking studies using bromodeoxyuridine substituted DRE confirmed that the 200-kDa protein bound to the DRE was the heterodimeric AhR complex. DIM also induced CYP1A1 mRNA levels in MCF-7 cells at concentrations > 50 μM. In contrast, DIM significantly inhibited E2-induced proliferation of MCF-7 cells at concentrations as low as 0.1 μM and reporter gene activity in MCF-7 cells transiently transfected with an estrogen-responsive construct. In parallel studies, DIM also exhibited antiestrogenic activity in the 21-day-old B6C3F1 at a dose of 100 mg/kg/day for 3 days; however, at this same dose, no significant induction of CYP1A1-dependent ethoxyresorufin O-deethylase (EROD) activity was observed. Results obtained for DIM resembled those previously reported for alternate substituted alkyl PCDFs: moderate to high AhR-binding affinity and antiestrogenic responses, both in vivo and in vitro, observed at doses significantly lower than required for induction of CYP1A1-dependent activity (a surrogate response for AhR-mediated toxicities).

Several rodent models are routinely used to assess the in vivo activity, and this includes the carcinogen-induced mammary tumor assay in female Sprague-Dawley rats. Administration of chemicals such as 7,12-dimethylbenzanthracene (DMBA) to 45–55-day-old rats results in formation of mammary tumors after 1.5 to 3 months, and the efficacy of antiestrogen drugs as inhibitors of mammary tumor growth can then be determined. Formation of these tumors is estrogen-dependent and in our studies, clinically used antiestrogens such as tamoxifen are effective at doses of 0.1 to 1.0 mg/kg/day. Studies with DIM in the DMBA-induced mammary tumor showed that tumor...
growth was completely inhibited at a dose of 5 mg/kg every second day (for 3 weeks). However, at lower doses (1 and 0.5 mg/kg), no significant inhibition was observed. At the effective dose, DIM did cause any change in organ weights or histopathology and hepatic EROD activity was not induced. These results are in contrast to inhibition of mammary tumor growth by the toxic halogenated aromatics such as TCDD or 3,3′,4,4′-tetrachlorobiphenyl in which organ and body weight changes are also accompanied by induction of hepatic CYP1A1-dependent activities (Ramamoorthy et al., 1999).

Current studies in this laboratory are investigating the anti-tumorigenic activity of relatively non-toxic SAhRMs including a series of symmetrically substituted DIMs as antitumorigenic agents. Results of initial in vivo screening indicate that some of these analogs are antitumorigenic at doses of ≤1.0 mg/kg every second day (i.e., ≤0.5mg/kg) and are more potent than tamoxifen in this in vivo rodent assay. It is to be hoped that AhR-based antiestrogens can be further developed as chemotherapeutic agents for treatment of breast cancer in women, and this receptor could be an important target for development of SAhRMs.

Organosulfur Compounds in Alliums: Mechanism of Chemopreventive Action (M. Wargovich)

The use of herbal supplements has dramatically increased in the United States during the last several years. At least 25% of U.S. households report that they use garlic frequently, either in cooking, or as a dietary supplement. Wargovich and coworkers have been involved in the evaluation of garlic as a cancer preventive for many years. These studies were prompted by initial reports that DMBA-initiated/TPA promoted skin tumor development was strongly inhibited by topical application of garlic oil (Perchellet et al., 1990).

Earlier studies suggested that diallyl sulfide (DAS), one of the volatile organosulfur compounds in garlic, was a potent inhibitor of chemical carcinogens activated by CYP2E1, namely, dimethylhydrazine-induced colon cancer and nitrosomethylbenzylamine-induced esophageal cancer (Wargovich, 1987; Wargovich et al., 1992). Studies directed to the mechanism of chemoprevention revealed that DAS and related garlic compounds strongly inhibit CYP2E1 at the protein and mRNA levels. Current studies are utilizing a structure-activity approach and the in vivo chemopreventive activity of common organosulfur volatiles from garlic and onion are being investigated. Garlic compounds tend to have allylic side chains in their structures whereas compounds from onions are more aliphatic (Fig. 1). Results of current research indicate that the allylic group is a determinant for CYP2E1 inhibition and the allylic compounds are more likely to prevent carcinogen-induced preneoplasia in the rat than the more volatile aliphatic compounds. However, sulfur compounds in allium vegetables influence more than one enzyme system. Studies focused on later stage effects of the garlic compounds suggest that allium compounds also influence metabolic detoxification pathways. For example, continual exposure of rats to DAS markedly elevated glutathione-S-transferase (GST) enzyme activities in the liver and intestine of exposed rats. Time course experiments indicate that induction of the GST enzyme is significantly elevated 48 h after treatment (Sumiyoshi and Wargovich, 1990). Additional studies in the laboratory point toward an induction of GST-α and β in the liver of DAS-treated rats. This phenomenon is not limited to allium vegetables but has also been observed when isothiocyanates from cruciferous vegetables was administered to animals. This biphasic ability of the garlic compounds to inhibit P450-mediated metabolism while stimulating phase II metabolic detoxication pathways presents an unique opportunity to determine if the balance of effects on these enzyme systems is an important determinant of chemoprevention of cancer.

Much of the chemistry of garlic is initiated when γ-glutamyl cysteine is converted to allicin. When the garlic clove is crushed, allicin is converted by a released enzyme known as allinase, into a variety of water and oil-soluble volatiles, as well as water-soluble sulfur compounds. These compounds, accounting in part for the odor and taste of garlic, are the focus of research on their potential as cancer preventives.

In addition, it has also been shown that case-control and cohort studies across the world support the notion that garlic and other allium vegetables reduce the risk for cancer in humans (Table 1). Epidemiological studies indicate that cancers of the colon and stomach are fewer in countries with higher daily use of garlic and other allium vegetables. However, studies in Holland show no support for the preventive aspects of garlic use in cancers of the breast and lung.

Genistein: in Vivo Mechanisms of Action and Chemoprevention (C. Lamartiniere)

The incidence of breast cancer is especially high in the Western world, while Asian women consuming a traditional diet high in soy have a low incidence of breast cancer (Lee et al., 1991; Rose, 1992; Setchell et al., 1984; Wu et al., 1996). However, when Asians emigrate to the U.S., the succeeding generations of Asians living in the U.S. lose this protection (Ziegler et al., 1993). This has prompted us to hypothesize that exposure to a component of soy, early in life, would confer a “programming” effect on the tissue to render a permanent protection against breast cancer. Programming is defined as developmental alterations occurring during an early critical period of life that results in a permanent manifestation, even in the absence of the original effector (Lamartiniere et al., 1982). The primary isoflavonic component of soy is genistein, a well-characterized inhibitor of protein tyrosine kinase (Akiyama et al., 1987; Dean et al., 1989) and topoisomerase II (Okura et al., 1988). In addition, it possesses antioxidant (Gyorgy et al., 1986) and estrogenic activities (Bickoff et al., 1962). The latter property may be related to the early program-
ming effects of genistein. We have demonstrated that treatment with genistein (500 μg/g) on days 2, 4, 6 postpartum, or prepubertal days 16, 18, 20, protected against dimethylben-
(2a)-anthracene (DMBA)-induced mammary cancer in rodents
(Lamartiniere et al., 1995a,b, 1998a,b; Murrill et al., 1996). Early postnatal administration of genistein enhanced mammary gland maturation and 50-day-old female rats treated with genistein had significantly fewer terminal end buds and slightly more lobules II compared to control animals. Terminal end buds are the least differentiated and most susceptible terminal ductal structures of the mammary gland to carcinogenesis, while lobules II are more differentiated and less susceptible to carcinogenesis (Russo and Russo, 1978a,b; Russo et al., 1988)

To gain insight into regulation of signal transduction by genistein, we investigated proteins of the epidermal growth factor (EGF) signaling pathway. The EGF receptor is a membrane-bound tyrosine kinase and both EGF and transforming growth factor α (TGFα) are ligands for this receptor. In 21-
day-old animals, prepubertal genistein up-regulated TGFα and EGF-receptor (but not EGF) expression in mammary terminal ductal structures (Brown et al., 1998). However, in 50-day-old animals, EGF-receptor immunostaining intensity was decreased in terminal end buds. Thus, stimulation of TGFα and the down-regulated EGF-signaling pathway in the terminal end buds and terminal ducts of adult mammary glands.
Rats were also exposed to more physiological dietary levels of genistein (0, 25, and 250 mg genistein/kg AIN-76A diet) from conception through day 21 postpartum. At day 50 post-
partum, all animals were treated with DMBA for induction of mammary cancer. Genistein in the diet resulted in dose-depen-
dent protection against the development of mammary tumors
(Fritz et al., 1998), and 21- and 50-day-old female rats had significantly fewer terminal end buds. These effects were not observed after only prenatal exposure to genistein (Lamartiniere, 1999) suggesting that protective “programmed” re-
sponses were observed only after dietary exposure to genistein during the early postnatal period.

Total blood levels of genistein (aglycone and conjugated
forms) in lactating female Sprague-Dawley rats administered 250 and 25 mg/kg HN-768 diet were 418 and 40 pmol/ml, respectively (Fritz et al., 1998), and milk levels were 137 and 67 pmol/ml, respectively, in 7-day post lactating dams. Higher levels of genistein were observed in the stomach milk (4439 and 490 pmol/ml, respectively) and blood (726 and 86 pmol/
ml, respectively) in 7-day-old rats. In 21-day-old rats nursing and fed the genistein-containing diets, total blood genistein concentrations were 1810 and 54 pmol/ml, respectively. Mam-
mary gland levels were 440 and 370 pmol/g tissue, respec-
tively (Fritz et al., 1998), and milk levels were 137 and 67 pmol/ml, respectively, in 7-day post lactating dams. Higher levels of genistein were observed in the stomach milk (4439 and 490 pmol/ml, respectively) and blood (726 and 86 pmol/
ml, respectively) in 7-day-old rats. In the DMBA-rat model, we observed mammary cancer prevention with one-thirtieth and one-third of that concentration. Hence, protection against chemically induced mammary cancer in rats can be achieved after short-term exposure (early postnatal) to concentrations of genistein that are lower than observed in the of 7- and 21-day-old rats. In the DMBA-rat model, we observed mammary cancer prevention with one-thirtieth and one-third of that concentration. Hence, protection against chemically induced mammary cancer in rats can be achieved after short-term exposure (early postnatal) to concentrations of genistein that are lower than observed in infants consuming soy-based formula. Genistein levels are significantly lower in fetuses (43 pmol/ml) than in dams on the high-concentration diet (250 mg/kg) (Lamarti-
riere, 1999). This finding suggests that failure to alter mam-
mary gland differentiation was due to low bioavailability and inability of conjugated genistein to cross the placental barrier to the fetus. Perinatal genistein in the diet did not significantly alter fertility in the F0 female rats, or in numbers of male and female offspring (Fritz et al., 1998), and histomorphological evaluation of the female reproductive tract was not affected.

Chemoprevention experiments in rats support epidemiolog-
ical data showing that Asian women consuming a diet high in soy are less susceptible to mammary cancer (Setchell et al., 1984) and (Lee et al., 1991; Rose, 1992; Wu et al., 1996; Ziegler et al., 1993). This protection can be achieved by early postnatal exposure to genistein in the diet. This is also consistent with the report that decreased breast cancer risk in human females is associated with first full pregnancy at an early age as

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**TABLE 1**

<table>
<thead>
<tr>
<th>Tumor site</th>
<th>Type of study</th>
<th>Result</th>
<th>Population</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach cancer</td>
<td>Case-control</td>
<td>OR* of 0.4 for highest quartile of consumers of allium vegetables</td>
<td>China</td>
<td>You et al., 1989</td>
</tr>
<tr>
<td>Stomach cancer</td>
<td>Case-control</td>
<td>OR of 0.6–0.8 for frequent consumers of garlic and onions</td>
<td>Italy</td>
<td>Buiatti et al., 1989</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>Case-control</td>
<td>OR of 0.72–0.77 for onion consumers</td>
<td>Australia</td>
<td>Steinmetz and Potter, 1993</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>Cohort</td>
<td>OR of 0.68 for consumers of garlic</td>
<td>United States</td>
<td>Steinmetz et al., 1994</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>Cohort</td>
<td>No effect on risk in users of garlic supplements or consumers of onion and leeks</td>
<td>The Netherlands</td>
<td>Dorant et al., 1995</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>Cohort</td>
<td>No effect on risk in consumers of allium vegetables</td>
<td>The Netherlands</td>
<td>Dorant et al., 1994</td>
</tr>
</tbody>
</table>

* OR = odds ratio.
compared to nulliparity (MacMahon et al., 1973). Cell replication in the human mammary gland is at its peak during early childhood and decreases considerably with age (Meyer, 1977). Women between the ages of 15 and 19 years are also more susceptible to ionizing radiation (Boice and Monson, 1977; McGregor et al., 1977), suggesting that the early period of a woman’s life is crucial for predisposition to or for protection against later breast cancer. Furthermore, future generations of Asians who emigrate to the U.S. lose this protection from breast cancer, and this may be related to lower early postnatal ingestion of soy food products (Ziegler et al., 1993). This protection has been observed with estrogen and progesterone (Grubbs et al., 1985), and early full-term pregnancy has also been associated with reduced risk for breast cancer (MacMahon et al., 1973). All of these reports suggest that early events in development may alter susceptibility for breast cancer and soy products appear to offer protection from this disease.

Green Tea in Chemoprevention of Cancer: Mechanism of Action (H. Mukhtar)

Background

Among numerous known potential chemopreventive agents, those present in the human diet have received considerable attention (Challa et al., 1997; Kelloff et al., 1996). The anticarcinogenic and antimutagenic properties of the polyphenolic agents present in green tea were first demonstrated from this laboratory (Khan et al., 1988; Wang et al., 1989a,b), and since then, extensive laboratory and epidemiological research has shown that green tea may protect against a variety of cancer types. Green tea, derived from the plant Camellia sinensis, an evergreen shrub of the Theaceae family, contains many polyphenolic antioxidants and is a popular beverage worldwide. For many generations, tea consumption has been believed to possess health-promoting potential (Weisburger et al., 1997). Tea is consumed at greatly varying levels in different parts of the world, with a per capita worldwide consumption of approximately 120-ml per day (Katiyar and Mukhtar, 1996). The major types of tea that are currently consumed include black tea (78%, mainly consumed in western countries and some Asian countries), green tea (20%, mainly consumed in China, Japan, India, and a few countries in North Africa and the Middle East), and oolong tea (2%, consumed in southeastern China and Taiwan) (Katiyar and Mukhtar, 1996). The cancer preventive potential of green tea has been attributed to polyphenolic antioxidants present in green tea and these include (-)-epicatechin, (-)-epigallocatechin, (-)-epicatechin-3-gallate, and (-)-epigallocatechin-3-gallate (EGCG) (Fig. 1). Much of the cancer chemopreventive effects of green tea have been attributed to the major polyphenolic constituent EGCG, other polyphenols and agents present in green tea also contribute to its cancer chemopreventive effects (Katiyar and Mukhtar, 1996).

Tea and Cancer Chemoprevention

Experimental and epidemiological research has provided convincing evidence that polyphenolic antioxidants present in green tea inhibit cancer initiation and its subsequent development (reviewed in Katiyar and Mukhtar, 1996). Studies have shown that oral consumption or topical applications of green tea and/or its polyphenolic constituents afford protection against chemical carcinogen- or ultraviolet radiation-induced skin carcinogenesis, and chemically-induced carcinogenesis in lung, forestomach, esophagus, duodenum, pancreas, liver, breast, and colon in animal models (reviewed in Katiyar and Mukhtar, 1996). Data presented in this symposium showed that EGCG also prevents prostate cancer.

Mechanism(s) of Biological Effects of Tea

A complete understanding of mechanisms and biological effects induced by green tea and/or its polyphenols may be helpful in designing better strategies for cancer prevention. Initial studies on mechanisms of green tea/polyphenol-induced biological responses were largely focused in the following areas (reviewed in Katiyar and Mukhtar, 1996):

i. inhibition of biochemical markers of tumor initiation,
ii. inhibition of biochemical markers of tumor promotion,
iii. prevention against mutagenicity and genotoxicity,
iv. antioxidant and free radical scavenging activity,
v. effects on detoxification enzymes, and
vi. trapping of activated carcinogen metabolites.

Green tea polyphenols in general and EGCG in particular affect a variety of targets/pathways, and this may be responsible for the exceptionally high cancer chemopreventive efficacy of these compounds in multiple tissues/organs. The targets/pathways modulated by green tea polyphenols and/or EGCG, which are believed to contribute to its anti-cancer property, include (i) MAPK, ERK2, JNK1; (ii) urokinase; (iii) apoptosis/ cell cycle; and (iv) protein tyrosine kinase (PTK) and ornithine decarboxylase (ODC) activities (Ahmad et al., 1997). Modulation of these responses has previously been reviewed in detail (Ahmad and Mukhtar, 1999). In this symposium, data was presented that implicated induction of apoptosis, alterations in cell cycle regulation and inhibition in NF-κ-B-activation as potential targets for the anticarcinogenic activities of green tea/polyphenols.

Summary

In recent years, it has been suggested that diet is responsible for about one-third of the cancers and, for this reason, the strategy of diet manipulation has become increasingly important as an approach for cancer prevention (Ahmad and Mukhtar, 1999; Katiyar and Mukhtar, 1996; Kohlmeier et al., 1997). The use of tea, especially green tea, for prevention of cancer has only been appreciated in the last ten years.
Tea is one of the most popular beverages in the world, and epidemiological and laboratory research has indicated that tea consumption possesses beneficial effects against development of many cancer types. Although compelling evidence is now available in favor of the cancer preventive potential of green tea, a clear understanding of the mechanisms of action is far from complete. As discussed above, it is clear that the green tea polyphenols may modulate multiple signaling pathways that may be responsible for development of cancer. Green tea appears to possess qualities of an ideal chemopreventive agent, since this beverage product (a) induces minimal or no toxic effects, (b) exhibits high efficacy at multiple sites, (c) can be taken by oral administration, (d) induces responses through multiple pathways, (e) has a low cost, and (f) is widely used in the human diet. In view of the available laboratory and epidemiological data, it would be reasonable to evaluate the usefulness of green tea polyphenols in clinical trials with humans. It is noteworthy that clinical trials for evaluating the efficacy of formulated green tea in patients with advanced solid tumors are currently being conducted at many centers around the world.

CONCLUSIONS AND FUTURE DIRECTIONS

The Symposium discussed the anticarcinogenic properties of four different structural classes of phytochemicals: DIM and related compounds from cruciferous vegetables, organosulfur compounds from allium, the isoflavone genistein, and polyphenolics from green tea. These compounds act through multiple biochemical pathways and can play a role in both cancer prevention and cancer chemotherapy. Since most human cancers are highly complex and tumors of the same type from different individuals can exhibit genotypic and phenotypic differences, it is important to continue development of multiple treatment regimens using individual and combined drug therapies. The anticarcinogenic properties of natural products such as taxol, macroclide antibiotics, and cytotoxic agents have been extensively used as models for developing new anticancer drugs, and the phytochemicals discussed in this symposium also provide new opportunities for mechanism-based drug design.

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