Soy, Its Components, and Cancer Prevention: A Review of the in Vitro, Animal, and Human Data

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Introduction

The incidence of breast, prostate, and colon cancer, among others, is lower in Asian countries than in the West. People living in China, Japan, and Korea, for example, are 4 to 10 times less likely to be diagnosed with and die from breast and prostate cancer than are people in the United States (1). Traditionally, migrant populations have been examined to determine how much of the difference between ethnic groups is due to genetic tendencies and how much is due to environmental factors. In one such study, cancer incidence was observed among Japanese peoples migrating to the United States (2). Within two generations of migration, cancer mortality rates increased to levels similar to the native Caucasian population. This suggests that environmental and behavioral factors may be more important than genetic factors in determining cancer frequency between populations. Based on epidemiological calculations by Doll and Peto (3, 4), as many as 75-80% of all fatal cancers in the United States are due to extrinsic factors and thus may be preventable.

Potentially avoidable environmental factors contributing to cancer frequency include diet, smoking, alcohol consumption, reproductive behavior, infection, geophysical factors including sunlight, and prolonged exposure to extrinsic agents such as fossil fuel combustion products, radioactive waste, dust and fumes, pesticide residues, and food additives (4). Diet, in particular, is one such factor that can vary significantly from country to country and has been estimated to account for up to 35% of all cancer rate differences (4). Although Western and Eastern diets vary widely, one striking distinction between them is the source of protein. Those in the West generally rely on animal protein, whereas Eastern diets emphasize bean, particularly soybean, as a protein source.

Soybeans have long been a major component of the Eastern diet. Asians consume an average of 20–80 g of soyfoods per day, whereas Americans eat only 1–3 g daily (5). Commonly consumed Asian soy products include soy milk, tofu, miso, yuba, and tempeh. Moreover, extensive epidemiological, in vitro, and animal data collected over the previous several years suggest that soybean consumption reduces the risk of developing several types of cancer including breast, prostate, and colon cancer. Alternatively, diets high in casein, animal fat, and calories correlate with increased cancer incidence (6, 7). Dietary soyfood intake has thus been proposed to contribute, at least in part, to these differences.

Preliminary experiments in animal models of carcinogenesis suggested that soy consumption decreases tumor number, incidence, latency, and metastasis. A review by Messina et al. (8) summarizes 26 such experiments carried out between 1975 and 1993. At least 17 of these reports (65%) indicate that soy supplementation has chemoprotective action. However, as the authors have suggested, a limitation of these studies is that a number of different soy preparations were used and thus the discrete action of relevant soy constituents is difficult to evaluate. More recently, the protective effects of isolated soy micronutrients such as isoflavones, protease inhibitors, saponins, and phytic acid have been evaluated. This review will examine the in vitro, animal, and human data surrounding the role of these soy components in cancer prevention. Several other papers have reviewed the potential actions of phytoestrogens in preventing cancer (9–12).

Potential Anticancer Constituents Found in Soybeans

Isoflavones. Isoflavones are a group of naturally occurring heterocyclic phenols found in soybeans and forage plants. Genistein (4',5,7-trihydroxyisoflavone) and daidzein (4',7-dihydroxyisoflavone), occurring as their β-glucosides genistin and daidzin, respectively, are the principal isoflavones found in soybeans consisting of as much as 90% of the total soybean isoflavone content (13). Soybeans are a particularly plentiful source of isoflavones with genistein and daidzein levels of up to 3 mg/g (14). Asian-style soy-based products (soy milk, tofu, soy flour, soy powder, and soy nuts) that are not diluted by other foods have total isoflavone concentrations in the range of 1.3–3.8 mg/g of dry weight (0.2–2.3 mg/g wet weight). In addition, fermented soy foods, usually prepared by mixing soy with other foods such as barley, rice, or wheat, contain isoflavone concentrations in the range of 0.6–1.4 mg/g of dry weight (0.3–0.8 mg/g wet weight) (14–16). On the basis of average annual consumption of soybeans, daily intake of genistin and genistin by the Japanese is calculated to be 1.5–4.4 and 6.3–8.3 mg/person, respectively (17).

Genistein commonly has been offered as the primary anticancer soy constituent based on putative in vitro activities including: estrogen antagonism (18); inhibition of protein tyrosine phosphorylation (19–22); inhibition of DNA topoisomerases I and II (23); suppression of angiogenesis (24); induction of differentiation in cancer cell lines (25, 26); inhibition of tumor promoter-induced hydrogen peroxide formation (27); induction of apoptosis (28, 29) scavenging of exogenous hydrogen peroxide free radicals; and antiproapoptotic effects (30). A possible caution to the indiscriminate use of isoflavones, however, is evidence that they possess antithyroid properties. Studies suggest that soybeans can inhibit thyroid peroxidase-catalyzed reactions essential to thyroid hormone

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1 To whom requests for reprints should be addressed, at Clinical Oncology and Chemoprevention, G. D. Searle & Co., 4901 Searle Parkway, Skokie, IL 60077.
synthesis (31) and that this inhibition can induce goiter, hypothyroidism, and thyroid neoplasia in rodents and humans (32–34).

Although the exact mechanism of cancer protective action has not been characterized, one hypothesis is that isoflavone phytoestrogens may reduce cancer risk by decreasing the promotion rate of thyroid hormone synthesis (35). Both genistein and daidzein bind to estrogen receptors (36, 37), including those on MCF-7 human breast cancer cell lines, although with weak estrogenic activity compared with 17β-estradiol. Thus, these isoflavones have been implicated as antigonadotropins through competition with endogenous estrogen for receptor binding. However, like most antiestrogens including tamoxifen, genistein exhibits paradoxical effects, either agonistic or antagonistic, depending on the species, tissue, and dose administered (38–40). These findings are particularly interesting in light of the recent discovery of an additional ERα subtype, ERβ, in certain rat (41), mouse (42), and human (43) tissues. ERβ, a novel member of the nuclear receptor superfamily, is highly homologous to the rat ER protein, particularly in the DNA-binding domain (95%) and in the COOH-terminus ligand-binding domain (55%) (44). The existence of ERβ subtypes vastly expands the physiological regulatory potential of estrogenic hormones. For example, different target cells may respond differently to the same hormonal stimulus, depending on the particular receptor composition. Varying ratios of ERα and ERβ proteins in different cells may result in different populations of homo- and heterodimers that account for yet unrecognized mechanisms involved in the tissue- and cell type-specific actions of estrogens and antiestrogens (44).

Saponins. Legumes, especially soybeans, are the major dietary source of saponins. Saponins are heat-stable glycosides composed of a lipid-soluble aglycone (consisting of either a sterol or triterpenoid) linked to one or more water soluble sugar residues (45, 46). The molecules are amphiphilic, the triterpenic part being hydrophobic and the sugar portion hydrophilic, giving them their characteristic surface activity (47). The chemical characteristics of saponins, including polarity, hydrophobicity, and acidity, are thought to be related to their biological activity, and recent in vitro evidence suggests that they are hypocholesterolemic (47–49), immunostimulatory (50, 51), anticarcinogenic (52–54), and scavengers of free radicals (55, 56). Proposed mechanisms of anticarcinogenesis include selective toxicity toward cancer cells, immune modulation, and regulation of cell proliferation (46).

Soybeans contain ~0.5% saponins, whereas soy products such as soymilk, tofu, and yuba contain saponins in the range of 0.3–0.4% (57). Saponin concentrations ranging from 150–600 ppm inhibited human carcinoma cells (HCT-15) in vitro (46), whereas 0.16 g of daily dietary saponin suppressed chemically induced colon cancer in CF1 mice (45). This concentration equates to about 6 g of defatted soy flour per day for humans, an amount well within range of the average Asian daily diet (45). Although saponins have strong hemolytic activity and are reportedly toxic in some fish and cold-blooded animals (58), no adverse effects were found when soy saponins were fed to chicks, mice, or rats (59). Additionally, when administered p.o. to rodents, most saponins, including those derived from soy beans, are not toxic (47).

Protease Inhibitors. Protease inhibitors are proteins found in cereals, nuts, vegetables, eggs, and potatoes with typical molecular weights between M, 8,000 and M, 10,000. As much as 6% of all soy protein consists of protease inhibitors, making them a particularly plentiful source (60). Soy-derived protease inhibitors suppressed neoplastic growth both in vivo and in vitro (61, 62), inhibited carcinogen and radiation-induced malignant transformation in vitro carcinogenesis-related end points, including proteolytic activities (61, 65, 66), oncogene expression (67–69), and gene amplification (70).

Two of the most extensively studied soy-derived protease inhibitors include the BBI and the soybean protease inhibitor (Kunitz inhibitor). BBI, an M, 8,000 polypeptide with seven disulfide bridges and two homologous inhibitory sites (60), is a very potent anticarcinogen with activity resulting from the inhibition of both trypsin and chymotrypsin (71, 72). Because the mechanism of carcinogenesis has not yet been fully elucidated, the exact anticarcinogenic action of BBI is unknown. However, Kennedy et al. (61) have suggested that protease inhibitors may suppress carcinogenesis via inhibition of specific oncogenes and proteases thought to be involved in the conversion of a cell from normal to malignant.

Both purified BBI and diets using soybean concentrate containing BBI suppress chemically induced colon cancer (73), lung cancer (74), oral cancer (75), and esophageal cancer (73) in vivo. For many of the animal studies using BBI concentrate, parallel studies with purified BBI yielded essentially the same suppressive effects. This suggests that most of the chemoprotective activity is due to the BBI (76). The lowest effective dietary concentrations of protease inhibitor used in animal studies (0.1% of total diet) is achievable in humans through dietary soy intake (77). It is important to note, however, that this extrapolation is based on the assumption that BBI is readily absorbed, intact, from the diet. However, Yavelow et al. (78) reported that although dietary BBI reaches the colon in active form, very little is taken up in the bloodstream and delivered to other organs. Thus, intake of large dietary quantities of BBI may result in high levels in the colon lumen and feces without a simultaneous increase in internal organ levels (79).

The soybean trypsin inhibitor, or Kunitz inhibitor (M, 21,000), is a second soy-derived protease inhibitor that has been well characterized. Unlike BBI, this inhibitor has primary activity against trypsin with only a slight ability to inhibit chymotrypsin. Several other soy-derived protease inhibitors have been identified but have not yet been characterized.

Inositol Hexaphosphate (PA). Inositol hexaphosphate or phytic acid is a naturally occurring compound found in plants, cereals, and legumes that appears primarily as a salt with monovalent and divalent cations (Ca++, Mg++, and K++; Ref. 80). Several recent studies indicate that PA may have anticarcinogenic properties including the ability to bind to iron and zinc ions (potentially decreasing iron-mediated cancer risk; Ref. 77), a suppressive effect on transition metal oxidant reactivity (decreasing radical generation; Ref. 81), the inhibition of lipid peroxidation (82), and as a second messenger involved in cellular proliferation and differentiation. Shamsuddin et al. (83) hypothesize that one of the ways inositol hexaphosphate exerts its antineoplastic and antiproliferative effect is through increasing intercellular levels of inositol triphosphate with a resultant decrease in cell division.

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2 The abbreviations used are: ER, estrogen receptor; BBI, Bowman-Birk inhibitor; PA, phytic acid; GI, gastrointestinal; SD, Sprague Dawley; MNU, N-methyl-N-nitrosourea; DMBA, dimethyl-benz[a]anthracene; AOM, azoxymethane; PB, phenobarbital; GGT, γ-glutamyltransferase positive; PGST+, placental glutathione S-transferase positive; AHF, altered hepatic foci; NMBzA, N-nitroso-p-phenylenediamine; NAF, naphthyl aspirate fluid; GCDFP, gross-cystic disease fluid protein.
Despite the *in vitro* and *in vivo* anticarcinogenic properties exhibited by PA, Zhou and Erdman (84) indicate that PA has an inhibitory effect on the bioavailability of several minerals including calcium, iron, and zinc. The suppressive effect of PA on calcium bioavailability has been attributed to the formation of insoluble PA-calcium complexes that are nonabsorbable in the GI tract (85, 86). In turn, insoluble PA-calcium complexes are thought to contribute to decreased bioavailability of zinc and iron by binding to these minerals and forming even less soluble complexes (84). Thus, research regarding beneficial anticarcinogenic properties of PA should be viewed in light of potential adverse effects on mineral bioavailability.

**Animal Studies**

Table 1 lists animal studies designed to observe the effects of soy components on chemically or genetically induced cancers. Among them, 16 of 17 (94%) positively altered tumor incidence and/or multiplicity.

**Mammary Carcinoma Models.** Five experiments in animals with chemically induced mammary carcinomas indicate an inhibitory effect on tumor incidence as a result of soy intervention. SD rats, 7 weeks of age, with MNU-induced mammary carcinomas were fed diets containing 2 or 10% soybean, 10% miso, or 10 mg or 50 mg Biochanin A (isoflavone) for 18 weeks. Tamoxifen, a commonly used hormonal agent in the treatment of breast cancer, was given in combination with these diets in a similar experimental schedule. The 10% miso diet significantly reduced tumor multiplicity, whereas the 10% miso diet in combination with 2.5 mg/kg tamoxifen significantly reduced the incidence and the multiplicity of mammary tumors (87).

Constantinou et al. (88) found a significant reduction in MNU-induced tumor incidence in SD rats treated with 0.8 mg genistein or 0.8 mg daidzein compared with controls (4.9, 4.9 and 6.7, respectively). Importantly, isoflavone treatments did not affect the weight of the animals. In a similar experiment (89), 0.8 mg of genistein marginally reduced MNU-induced tumor incidence and multiplicity (*P* < 0.09). The high dose of daidzein (0.8 mg) decreased tumor multiplicity without affecting incidence, whereas the low dose (0.4 mg) was ineffective.

Lamartiniere et al. (90) studied short-term exposure to genistein during the first week postpartum to assess whether it exerts a life-long protective effect against mammary cancer. Three, 5-mg s.c. injections of genistein, the maximal deliverable dose without adverse effect on body weight, significantly inhibited DMBA-induced mammary tumor multiplicity *versus* control (6.4 ± 0.7 *versus* 3.7 ± 0.4) in SD rats. Mean times to detection of palpable tumors in animals treated neonatally with the vehicle DMSO, as compared with genistein, were 87 ± 37 days and 124 ± 33 days, respectively. Furthermore, animals treated with genistein consistently showed lower tumor incidence relative to age-matched controls (88% *versus* 100%) at 190 days post-DMBA exposure.

Finally, Murrill et al. (91) investigated the potential chemoprotective activity of genistein against DMBA-induced mammary cancer. Female SD rats were given genistein injections s.c. (500 µg/g body weight) on days 16, 18, and 20 postpartum or the same amount of DMSO vehicle. At day 50 postpartum, animals were exposed to 80 µg of DMBA per g of body weight. Serum genistein concentrations in animals 21 and 50 days of age after genistein treatment were 4.2 ± 0.6 µM and 102 ± 30 nM, respectively. Additionally, isoflavone treatment resulted in a reduction in incidence and a significant reduction in multiplicity of adenocarcinomas (data not provided). Mammary whole mounts indicated that prepubertal genistein treatment alters the ontogeny of mammary gland maturation and cell proliferation. In this respect, prepubertal genistein treatment has been hypothesized to accelerate terminal differentiation of the mammary gland, resulting in a decreased susceptibility to DMBA-induced carcinogen.

**Colon Cancer Models.** Four animal experiments found in the literature were protective for chemically induced colon cancer, whereas a fifth resulted in increased multiplicity of colonic adenocarcinomas. Kennedy et al. (92) examined whether BBI has the ability to affect intestinal carcinogenesis in the Min mouse model. Min mice have an autosomally dominant inherited predisposition to multiple intestinal neoplasms and are known to have a high rate of spontaneous tumor development in both the colon and intestine. 0.5% BBI concentrate administered in the diet led to a 42–50% reduction in the number of tumors per mouse in the small intestine and colon and a 41% reduction in tumorigenesis in the colon alone.

Koratkar and Rao (45) found that a diet containing 3% soy saponins, when administered 1 week after a last AOM injection, reduced the average number of aberrant crypt foci per colon in CFI mice as compared with controls (2.6 *versus* 7.67). Moreover, Billings et al. (72) inhibited dimethylhydrazine-induced colon carcinogenesis with BBI. In this study, diet containing 0.1% BBI reduced the incidence of adenocarcinomas of the colon by ~50%, but had no effect on squamous cell carcinoma of the anal gland. Autoclaved BBI (100% of the chymotrypsin activity destroyed) was ineffective at suppressing adenocarcinomas, indicating that protease inhibitor activity is critical for the suppressive effect.

In a study by Steele et al. (93), genistein decreased aberrant crypts in the colon of F344 rats treated with AOM. Dietary genistein was administered for 5 weeks, from 1 week before AOM administration to 4 weeks after. All animals were sacrificed at the end of AOM administration. At genistein amounts of 75 and 150 mg/kg diet, the mean number of foci per colon was significantly reduced by 29.3 and 34.1%, respectively. However, a dose response was not observed due to the marginal difference between the two treatment groups.

Similarly, Rao et al. (94) studied the effects of dietary genistein on AOM-induced colon cancer in male F344 rats. At 5 weeks of age, animals were fed control (AIN-76A) diet or diet containing 250 ppm genistein. Beginning 2 weeks later, all animals except those in the vehicle-treated group were given weekly s.c. injections of AOM (15 mg/kg body weight) for 2 consecutive weeks. Rats were continued on their respective dietary regimen for 52 weeks after AOM treatment and then were sacrificed. In contrast with the other colon cancer models, administration of genistein significantly (*P* < 0.01) increased noninvasive and total adenocarcinoma multiplicity compared with the control diet, but it had no effect on colon adenocarcinoma incidence nor on the multiplicity of invasive adenocarcinoma (*P* > 0.05).

**Prostate Cancer Models.** Four studies found in the literature indicate that soy components can exert a protective effect against prostate cancer. Male Copenhagen rats s.c. injected with Mat LyLu cells were given genistein p.o. or via i.p. injection. Although oral administration did not inhibit tumor growth, i.p. injection of 0.143, 0.285, and 0.428 mg/kg/day resulted in tumor weight reduction of 26% (*P* = 0.368), 9, and 11%, respectively, when compared with controls (95).

Mäkelä et al. (96) demonstrated inhibition of diethylstilbestrol-induced prostate cancer in Han:NMRI male mice. The animals were fed diets containing 7% roasted soybean. After 9...
<table>
<thead>
<tr>
<th>Author et al. (87), 1996</th>
<th>Rat/SD</th>
<th>F</th>
<th>Soybean meal: A (10 mg/g, 50 mg/kg); soy: (20%, 10%), miso paste: (10%); miso + TAM: (10% + 2.5 mg/g), TAMB: (2.5 mg/g);</th>
<th>Day 42 pp</th>
<th>Mammary</th>
<th>MNU</th>
<th>Week 7 pp</th>
<th>C = 90%. T&quot; = 89%, 68%. T&quot; = 83%, 73%. T&quot; = 75%. T&quot; = 48%. T&quot; = 68%.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constantinou et al. (88), 1996</td>
<td>Rat/SD</td>
<td>F</td>
<td>Genisteinβ, diadzein: 0.8 mg i.p., qd × 180</td>
<td>Day 35 pp</td>
<td>Mammary</td>
<td>MNU</td>
<td>Day 50 pp</td>
<td>C = 100%. T&quot; = 89%. T&quot; = 67. T&quot; = 49. T&quot; = 49.</td>
</tr>
<tr>
<td>Constantinou et al. (89), 1996</td>
<td>Rat/SD</td>
<td>F</td>
<td>Genisteinβ, diadzein: 0.4 mg or 0.8 mg i.p., qd × 180</td>
<td>Day 22 pp</td>
<td>Mammary</td>
<td>MNU</td>
<td>Day 50 pp</td>
<td>Marginal reduction with 0.8 mg genistein</td>
</tr>
<tr>
<td>Lamantin et al. (90), 1995</td>
<td>Rat/SD</td>
<td>F</td>
<td>Genistein: 5 mg</td>
<td>s.c. qod × 5</td>
<td>Day 22 pp</td>
<td>Mammary</td>
<td>DMBA</td>
<td>Day 50 pp</td>
</tr>
<tr>
<td>Murrill et al. (91), 1995</td>
<td>Rat/SD</td>
<td>F</td>
<td>Genistein: 500 μg/g bw</td>
<td>s.c. qod × 5</td>
<td>Day 16 pp</td>
<td>Mammary</td>
<td>DMBA</td>
<td>Day 50 pp</td>
</tr>
<tr>
<td>Kennedy et al. (92), 1996</td>
<td>Mice/Min</td>
<td>M &amp; F BBIC: 0.1%, 0.5%</td>
<td>Diet</td>
<td>In utero</td>
<td>Colon</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Kornaker and Rao, (45) 1997</td>
<td>Mice/CF1</td>
<td>M</td>
<td>Soybean saponin: 3%</td>
<td>Diet</td>
<td>1 week after last AOM</td>
<td>Colon</td>
<td>AOM</td>
<td></td>
</tr>
<tr>
<td>Billings et al. (72), 1990</td>
<td>Mice/C57BL/6</td>
<td>M</td>
<td>BBI: 0.1%, 0.01%, 0.0005% Aβ/1.0%</td>
<td>Diet</td>
<td>Week 8 pp</td>
<td>Colon</td>
<td>DMH</td>
<td>Week 10 pp</td>
</tr>
<tr>
<td>Steele et al. (93), 1995</td>
<td>Rat/F344</td>
<td>M</td>
<td>Genistein: 75% or 150% mg/kg diet</td>
<td>Diet</td>
<td>Week 7 pp</td>
<td>Colon</td>
<td>AOM</td>
<td>Week 8 pp</td>
</tr>
<tr>
<td>Rao et al. (94), 1997</td>
<td>Rat/F344</td>
<td>M</td>
<td>Genistein: 250 ppm</td>
<td>Diet</td>
<td>Week 5 pp</td>
<td>Colon</td>
<td>AOM</td>
<td>Week 7 pp</td>
</tr>
<tr>
<td>Naik et al. (95), 1994</td>
<td>Rat/Copenhagen</td>
<td>M</td>
<td>Genistein: 0.143, 0.285, 0.428 mg/kg/day</td>
<td>i.p. qd × 10</td>
<td>Day 4 pp</td>
<td>Prostate</td>
<td>MAT-LyLu cells</td>
<td>Day 0 pp</td>
</tr>
<tr>
<td>Makela et al. (96), 1996</td>
<td>Mice/Han-NMR</td>
<td>M</td>
<td>Soybean meal: 7%</td>
<td>Diet</td>
<td>Day 44 pp</td>
<td>Prostate</td>
<td>DES</td>
<td>Day 1 pp</td>
</tr>
<tr>
<td>Pollard and Luckett (97), 1997</td>
<td>Rat/Lobund-Wistar</td>
<td>M</td>
<td>Isoflavone: 1.69 mg/g protein (pre-MNU); (post-MNU)</td>
<td>Diet</td>
<td>9 wks pp or 13 wks pp</td>
<td>Prostate</td>
<td>MNU</td>
<td>Week 12 pp</td>
</tr>
<tr>
<td>Zhang et al. (98), 1997</td>
<td>Rat</td>
<td>M</td>
<td>Soy flour: 33%</td>
<td>Diet</td>
<td>Posttransplant</td>
<td>Prostate</td>
<td>Implanted tumor cells</td>
<td></td>
</tr>
<tr>
<td>Lee et al. (99), 1995</td>
<td>Rat</td>
<td>F</td>
<td>Isoflavone: 920 or 1840 μmol/kg</td>
<td>Diet</td>
<td>At weaning</td>
<td>Liver</td>
<td>DEN-PB-P</td>
<td>Day 10 pp</td>
</tr>
<tr>
<td>von Hofs et al. (73), 1991</td>
<td>Rat/SD</td>
<td>M</td>
<td>BBI: 180 mg</td>
<td>Diet</td>
<td>1 week prior to carcinogenesis</td>
<td>Lung cancer</td>
<td>NMBzA</td>
<td></td>
</tr>
<tr>
<td>Menon et al. (100), 1998</td>
<td>Mice/C57BL/6</td>
<td>M</td>
<td>Genistein: 200 μmol/kg bw</td>
<td>p.o. qod × 20</td>
<td>At B16F-10 inoculation</td>
<td>Lung</td>
<td>B16F-10 melanoma</td>
<td>NMBzA</td>
</tr>
</tbody>
</table>

* Greek superscripts relate the particular soy treatment/dose administered with the corresponding outcome (tumor incidence and multiplicity).

** T treatment: C, control; i.p., intraperitoneal injection; s.c., subcutaneous injection; p.o., oral administration; qd, every other day; qd, each day; ↓, decreased; ↑, increased; pp, postpartum; bw, body weight; NA, not applicable; TAM, tamoxifen; BBIC, BBI concentrate; AβBI, autoacclaved BBI; DES, diethylstilbestrol; DEN, diethylnitrosamine.
months of treatment, both the number of animals with dysplasia and the severity of changes in the dysplastic epithelium were reduced in animals consuming soy meal versus control. After 12 months of treatment, more animals in both groups showed severe dysplasia, and there were more dysplastic sites per animal. No significant differences were found between the treated and control groups after 12 months.

Pollard and Luckert (97) examined the effects of isoflavones (in soy protein isolates) on the development of prostate-related cancers in L-W rats. At 3 months of age, the rats were inoculated with MNU (30 mg/kg body weight i.v.), and 7 days later, each was twice implanted s.c. at 2-month intervals with testosterone propionate (25 mg) to reduce the intensity of the tumorigenic response. Animals were fed high (1.69 mg/g protein) and low (0.109 mg/g protein) isoflavone-supplemented diets at two stages of tumorigenesis: (a) starting 3 weeks prior to MNU inoculation; and (b) starting 7 days after administration of MNU, for the duration of the experiments. Treated and control rats were examined at frequent intervals for palpable P-SV tumors, which were detectable when 0.5 cm in diameter. In rats fed the high isoflavone-supplemented soy diet before initiation, the incidence of induced prostate cancer was reduced, and the disease-free period was prolonged by 27% compared with rats fed the same diet but low in isoflavones. Rats fed the same diets, started after MNU initiation, developed similar but less consistent results.

Zhang et al. (98) investigated the effect of soy flour on the development of prostatic adenocarcinoma in rats. Dunning R3327 PAP prostate tumors were transplanted in 125 rats, and tumor development was monitored during treatment with diets containing 33% soy flour, rye bran, heat-treated rye bran, and rye endosperm. The rats were treated for 24 weeks with 25 rats in each dietary group. In the soy flour-fed group, tumors were retarded during the first 16 weeks after transplantation compared with the control, fiber-free dietary group (P < 0.05). Body weights were lower during the 16 weeks after transplantation in the soy-fed group compared with control (P < 0.05). However, when tumor volume was adjusted for body weight, there was still significantly lower tumor volumes in the soy-fed group compared with control animals (P < 0.05). A significant increase in daily urinary excretion of isoflavonoids was also observed.

Hepatocellular Carcinoma Models. Lee et al. (99) used diethylaminoethane (15 mg/kg body weight) to initiate liver cancer in F344 rats at 10 days of age and at weaning; PB (500 mg/kg), a hepatocellular carcinoma promoter, was fed to one-half of the rats. Soybean isoflavones were fed to animals at two levels, 920 and 1840 mol/kg diet, for 3 and 11 months during PB treatment. Control rats were fed a diet without PB and with or without isoflavones. Soybean isoflavone extract at both levels normalized total hepatic glutathione peroxidase activity, which was suppressed ~17% by PB (P < 0.05). Both doses of isoflavone extract suppressed PB promotion of hepatocarcinogenesis, decreasing the volume occupied by GGT + and placental GST + AHF (P < 0.05) after 3 months. After 11 months of PB promotion, the 920 mol/kg isoflavone diet decreased PGST + AHF compared with the PB-fed control group, but neither isoflavone dose inhibited the development of GGT + AHF compared with the group fed PB alone. Conversely, the control group fed isoflavone extract at 1840 mol/kg diet displayed greater development of GGT + and PGST + AHF than the group fed the basal diet alone, indicating a cancer-promoting effect. Thus, this experiment provides support for the anticarcinogenic effect of isoflavones at lower doses but indicates the possibility of a narrow margin of safety.

Esophageal/Lung Cancer Models. A study by von Hofe et al. (73) found BBI to be protective against esophageal neoplasms induced by NMBzA in SD rats. NMBzA is a potent and organ-specific laboratory carcinogen that produces papillomas, dysplasia, and carcinomas. Animals were given 180 mg of dietary BBI three times per week during the week prior to carcinogen administration. Whereas induction of various neoplastic changes were significantly suppressed in BBI-treated animals versus those receiving NMBzA alone, the most significant decrease was observed in the number of simple hyperplastic lesions per animal (63 versus 110). The number of hyperkeratotic lesions (58 versus 93), papillomas (30 versus 54), dysplastic lesions (38 versus 60), and the number of lesions with lymphocytic infiltrate (56 versus 90) were also significantly lower in BBI-treated animals compared with control. Although there were nearly one-half the number of carcinomas per animal in the NMBzA/BBI group compared with the NMBzA group (6 versus 11 in 34 animals), this difference was not statistically significant.

Menon et al. (100) examined the effect of genistein and daidzein on the inhibition of lung metastasis induced by B16F-10 melanoma cells in C57BL/6 mice. Genistein, administered at 200 μmol/kg body weight, significantly inhibited lung tumor nodule formation by 53.6%. The lung collagen hydroxyproline content and the serum sialic acid level, a marker of metastasis, were also significantly lower than control animals (47.7%, P < 0.001). Daidzein had no significant effect on the reduction of lung metastasis.

Studies in Humans

To date, no human cancer intervention trials including soy components have been completed. Rather, initial human studies on soy intake and chemoprevention have focused on epidemiological associations, pharmacokinetic properties of soy components, the alteration of surrogate biomarkers (SBs) thought to be relevant to cancer prevention, and on the effects of isoflavones on circulating hormone levels. Table 2 outlines these reports.

Epidemiology. A number of epidemiological and migrant studies suggest that a decreased risk of breast cancer (101), prostate cancer (102), stomach cancer (103), colorectal cancer (104), lung cancer (105), and endometrial cancer (106) is associated with soybean consumption. Reviews of these reports have been published (8, 107) and, subsequently, will not be detailed here. It should be noted, however, that potential obstacles encountered by many of these studies, including variations in the type and amount of soy consumed, the inability to separate soy from other dietary variables, difficulties in relating particular dietary intake to the development of cancer several decades later, the inherent inaccuracy of questionnaire-based soy intake measurements, and contradictory study outcomes have led to inconclusive results, overall.

In contrast with epidemiological reports relying primarily on data retrieved from nutritional questionnaires, a recent case-control study by Ingram et al. (108) examined the association between phytoestrogen intake, as measured by urinary excretion, and subsequent cancer risk. Urine and blood samples were taken from women with newly diagnosed early breast cancer before any treatment started. The samples were assayed for daidzein, genistein, equol, enterodiol, enterolactone, and matairesinol. Controls were randomly selected from the electoral role after matching for age and residential area. After adjust-
ment for other risk factors, high excretion of both equol and enterolactone was associated with a substantial and significant reduction in breast cancer risk. Difficulties with the genistein assay prohibited analysis of this isoflavone. These data support prior observational studies that reported higher phytoestrogen excretion among populations with a low frequency of breast cancer (9, 109, 110).

**Isoflavone Pharmacokinetic Studies.** Lu et al. (111) examined urinary excretion of isoflavones in healthy volunteers consuming soymilk. Subjects 22–29 years of age were provided a low soy diet followed by 36 or 60 ounces of soymilk (13–14 mg of isoflavone/12 ounces with 15–19% as aglycones) daily for four days. Urine samples were collected each day. Approximately 75–100% of ingested daidzein and 15–60% of ingested genistein were excreted as glucuronides in the urine within 20 h of consumption. Peak urinary levels of both compounds were attained 5–12 h after ingestion, suggesting that these isoflavones are readily absorbed and excreted in the urine.

In a similar experiment (35), the kinetics and extent of urinary isoflavone excretion were examined in women during chronic soy exposure. Six healthy women, 22–29 years of age, were given an unrestricted hospital diet and 12 ounces of soymilk with each meal for 1 month. At 2-week intervals, urinary isoflavone excretion was studied, during which time the subjects consumed a constant basal diet for 3–4 days, ingested a full daily 36-ounce serving of soymilk within 30 min for 1–2 days, and collected urine continuously. Urinary recovery of genistein (initially 23.9 ± 17.5% ingested genistin + genistein), daidzein (initially 66.2 ± 23.5% of ingested daidzin + daidzein), and equol (initially 28% of the ingested precursors

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Study type</th>
<th>Subjects</th>
<th>Soy product</th>
<th>Duration</th>
<th>Summary of results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ingram et al. (108) 1997</td>
<td>Case-Control</td>
<td>Females: 144 breast cancer patients, 144 controls</td>
<td>Urine samples were assayed for daidzein, genistein, equol, enterodiol, enterolactone, and matairesinol</td>
<td>NA</td>
<td>High excretion of equol and enterolactone was associated with a substantial reduction in breast cancer risk. Assay difficulties prevented analysis of genistein.</td>
</tr>
<tr>
<td>Lu et al. (111), 1993</td>
<td>Absorption/Excretion</td>
<td>36 or 60 ounces of soymilk; 13 or 14 mg of isoflavone/12 ounces daily</td>
<td>4 days</td>
<td>75–100% of ingested daidzein and 15–60% of ingested genistein was excreted within 20 h.</td>
<td></td>
</tr>
<tr>
<td>Lu et al. (35) 1996</td>
<td>Excretion</td>
<td>6 Females</td>
<td>12 ounces of soy milk/day</td>
<td>1 month</td>
<td>Urinary genistein recovery decreased progressively, whereas equol recovery increased with soy intake. Absorption and excretion ((k_{12})) is decreased.</td>
</tr>
<tr>
<td>Franke and Custer (114), 1994</td>
<td>Excretion</td>
<td>6 Females 5 Males</td>
<td>44–96 g of roasted soybeans during 1 day</td>
<td>3 days</td>
<td>Urinary recovery of daidzein, genistein, equol, and O-Dma, combined, ranged from 4–24% of total ingested soy dose as measured the first night after ingestion. Vast interindividual differences were observed for total amounts excreted.</td>
</tr>
<tr>
<td>Kelly et al. (115), 1993</td>
<td>Excretion</td>
<td>12 Males and Females</td>
<td>40 g of soya flour in a prepared cake</td>
<td>5 days</td>
<td>Urinary excretion of daidzein, genistein, and glycitein showed moderate variation among the 12 individuals. Urinary excretion of equol, O-Dma, and 6' OH-O-Dma showed more marked variation. Plasma isoflavone levels were increased significantly in soy-fed subjects compared with controls.</td>
</tr>
<tr>
<td>Gooderham et al. (118), 1996</td>
<td>Absorption</td>
<td>20 Males</td>
<td>60 g per day of soy protein isolate</td>
<td>28 days</td>
<td>Soy supplementation resulted in increased follicular phase length, delayed menstruation, suppressed midcycle LH and FSH surges, increased plasma estradiol concentrations, and decreased cholesterol.</td>
</tr>
<tr>
<td>Cassidy et al. (123), 1994</td>
<td>Hormone</td>
<td>6 Females</td>
<td>60 g of soy protein (45 mg of isoflavones)</td>
<td>1 month</td>
<td>Decreases were observed in serum 17β-estradiol, luteal phase progesterone, and dehydroepiandrosterone sulfates levels. Menstrual cycle length increased.</td>
</tr>
<tr>
<td>Lu et al. (124), 1996</td>
<td>Hormone</td>
<td>6 Females</td>
<td>12 ounces of soymilk (100 mg of both genistein and daidzein) 3 X/day</td>
<td>1 month</td>
<td>NAF volumes increased in premenopausal women on soy diet, no change was observed in postmenopausal subjects. GCDFP-15 decreased by 30% in postmenopausal subjects.</td>
</tr>
<tr>
<td>Petraitis et al. (127), 1996</td>
<td>Biomarker</td>
<td>24 Females</td>
<td>38 g of soy/day (38 mg of genistein)</td>
<td>12 months</td>
<td>Urinary isoflavone levels and breast lobular epithelium proliferation rate increased.</td>
</tr>
<tr>
<td>McMichael-Phillips et al. (131), 1996</td>
<td>Biomarker</td>
<td>Females with benign or malignant breast disease</td>
<td>60 g of soy (45 mg of isoflavones)</td>
<td>14 days</td>
<td></td>
</tr>
</tbody>
</table>

*O-Dma, O-desmethylangolensin; 6'OH-O-Dma, 6'-hydroxy-O-desmethylangolensin; LH, luteinizing hormone; FSH, follicle-stimulating hormone.*
daidzin + daidzein in one subject and <1% in 5 subjects) decreased progressively over 4 weeks by 42 and 31%, respectively, but increased 3- to 100-fold for equol (P < 0.05), an estrogentic daidzein metabolite. Absorption half lives (t1/2) decreased from 2.7 to 2.0 h (P = 0.04) for genistein and 1.6 to 1.4 h (P = 0.06) for daidzein, indicating more rapid absorption, whereas excretion t1/2 values decreased from 6.7 to 4.2 h (P = 0.005) for genistein and 4.4 to 3.2 h (P = 0.005) for daidzein during soymilk intake. These results suggest that the metabolism of ingested isoflavones is variable in women during chronic soy intake, perhaps as a result of receptor saturation or induced metabolism.

In contrast with these findings, several other papers have reported much lower urinary isoflavone recoveries (3%–10%) following ingestion of a soy-containing diet (112–116). It has been suggested that discrepancies in isoflavone recovery may be a result of calculation methods, purification processes, timing of urinary excretion, or alterations in the metabolism and disposition of isoflavones due to dietary influence (117). Franke and Custer (114) observed urinary isoflavone excretion in 11 individuals following challenge with 44–96 g of roasted soybeans. Urine was collected during the first and second nights after soy intake. Large variations in urinary recovery were found between individuals, ranging from ~4–24% based on total urinary amounts of genistein, daidzein, equol and O-desmethylangolensin. Similarly, Kelly et al. (115) reported moderate variation in urinary excretion rates of daidzein, genistein, and glycitein in 12 subjects after soy challenge.

Gooderham et al. (118) examined the effects of genistein and daidzein on plasma isoflavone concentration, blood lipids, and fatty acid composition of plasma phospholipid in healthy men. Twenty male subjects consumed either soy protein isolate beverage powder (60 g/day for 28 days) or control diet supplemented with casein. Plasma isoflavone levels increased significantly in the soy-supplemented group: genistein reached 907 ± 245 nmoI/l (110-fold increase), and daidzein reached 498 ± 102 nmoI/l (150-fold increase). Plasma total and HDL-cholesterol levels were not affected by soy feeding, although the subjects had normal cholesterol levels upon initiation. Similarly, plasma phospholipid polyunsaturated fatty acid composition showed no differences between groups.

In addition to measuring isoflavone levels in urine and plasma, investigators have examined the potential availability of isoflavones and their metabolites in human breast fluid. Breast feeding has known benefits to the mother (by protecting against ovarian and breast cancer) and to the infant (by protecting against various diseases and infections). To assess the exposure of newborn babies to these agents, Franke et al. (119) measured isoflavones in human breast milk. After moderate soy challenge, mean total isoflavone levels of 0.2 μm were reported in breast milk. In conjunction with the finding that cancer incidence and severity is significantly reduced when newborn animals are treated with genistein (120), these data suggest a cancer preventive effect of breast feeding to the offspring when mothers consume soy foods due to the exposure of the known anticancer isoflavones to the infant.

To date, human isoflavone pharmacokinetic studies suggest that genistein and daidzein are readily absorbed and excreted from the human body. Experiments in animals also indicate that soybean isoflavones may undergo enterohemepatic circulation (121). After moderate soy challenge, isoflavones have been measured in human urine, plasma, feces, and breast milk. Preliminary results indicate that urinary and plasma isoflavone levels are significantly increased during chronic soy intake, although a high degree of inter-individual variability has been measured. On the basis of epidemiological data, it has been suggested that as little as one serving of soy daily (4 ounces of tofu containing approximately 36 mg of isoflavones) may lower cancer risk. Pharmacokinetic figures suggest that isoflavones ingested from soy-protein isolate are bioavailable at amounts as low as 9 mg/day, a quantity roughly equal to 1 ounce of tofu (116).

Premenopausal Hormone Studies. Several in vivo and in vitro studies suggest that soybean isoflavones can act as phytoestrogens with either agonistic or antagonistic properties (38–40, 122). In addition, it has been noted that women living in countries with low breast cancer incidence have decreased circulating estrogen levels and longer menstrual cycles (107). Extrapolation from such studies suggests that significant modifications to the hormonal status of the menstrual cycle may beneficially alter risk factors for breast cancer. Accordingly, recent human studies have examined the effects of isoflavones on these parameters.

The influence of soy protein diet on hormonal status and menstrual cycle regulation was examined in six premenopausal women with regular ovulatory cycles in a controlled dietary study (123). Sixty g of soy protein (45 mg of isoflavone) administered daily for 1 month increased follicular phase length (17.50 ± 2.30 days to 15.00 ± 0.90 days) and/or delayed menstruation and significantly suppressed midcycle surges of both luteinizing hormone (7.1 ± 2.6 to 21.2 units/l ± 12.7) and follicle-stimulating hormone (7.8 ± 4.6 to 14.6 ± 5.6). Surprisingly, plasma estradiol concentrations increased during the follicular phase in subjects consuming isoflavone (data not provided).

Lu et al. (124) examined the effects of soy consumption on steroid hormone levels in six healthy women, ages 22–29 years. Beginning within 6 days of the onset of menses, subjects consumed a 10-ounce serving of soymilk (containing approximately 100 mg each of genistein and daidzein) three times daily for one month. Serum 17β-estradiol levels on cycle days 5–7, 12–14, and 20–22 decreased by 31% (P = 0.09), 81% (P = 0.03), and 49% (P = 0.02), respectively. After cessation of soy feeding, these decreases persisted for two to three menstrual cycles. Luteal phase progesterone levels decreased by 35% (P = 0.002), while dehydroepiandrosterone sulfate levels decreased progressively by 14–30% (P = 0.03) during soy feeding. Additionally, menstrual cycle length increased during the month of soy intake from 28.3 ± 1.9 days before consumption to 31.8 ± 5.1 days during consumption (P = 0.06). Total menstrual cycle length remained increased at 32.7 ± 8.4 days (P = 0.11) for one cycle after termination of soymilk feeding. Five to six cycles later, prefeeding cycle lengths resumed.

Biomarker Studies. The effects of soy feeding on cancer-related surrogate end points are presently being examined in human studies. Such indicators include breast fluid secretion, epithelial proliferation, cancer-specific antigens, plasma metabolite concentration, ductal carcinoma in situ, number and grade, nuclear morphometry, and estrogen receptor status. NAF has been examined as a potential marker for breast cancer because aspiration is a quick, efficient, noninvasive method of obtaining breast epithelial cells, the cells at risk for transformation to carcinoma. Results from studies by Sauter et al. (125, 126) indicate that prostate-specific antigen, a protein thought to be specific to the prostate, was recently found in a subset of breast tumor cells. Moreover, abnormal NAF cytology was found to correlate with increased breast cancer risk (P = 0.002); the percentage of cells in G0-G1 phase (P = 0.05), DNA index (P = 0.0002), and percentage of cells with hypertet-
estradiol concentrations were abnormally elevated during soy exposure to soy protein isolate on NAF in 24 women. GCDPF-15 concentration, NAF volume, and NAF cytology were used as biomarkers of possible effects of soy protein isolate on the breast. Subjects consumed 38 g of soy (38 mg of genistein) per day during months 4–9, whereas months 1–3 and 10–12 were control periods. During soy ingestion, NAF volumes increased 2–6-fold in 14 premenopausal women and in three postmenopausal women using replacement estrogen. In contrast, no change was noted in seven postmenopausal women not undergoing estrogen replacement. Of potential concern was the occurrence of hyperplastic epithelial cells within the NAF of 7 of 24 women during soy intake. In addition, plasma estradiol concentrations were abnormally elevated during soy feeding as compared with control. However, mean gross cystic disease fluid protein-15 (GCDPF-15 or BRST-2) concentrations, a specific and sensitive marker of primary and metastatic apocrine breast cancer (128-130), decreased 30% in premenopausal women compared with control. No changes were seen in plasma concentrations of prolactin, sex hormone-binding globulin, total cholesterol, HDL cholesterol, and triglycerides.

McMichael-Phillips et al. (131) examined the effects of soy supplementation on the proliferation rate of normal breast epithelium in premenopausal females. Women with benign or malignant breast disease were given placebo or 60 g of soy (45 mg of isoflavones) supplementation over the course of 14 days. Normal breast biopsies were labeled with [1H]thymidine to detect the number of cells in S-phase and stained for the proliferation antigen Ki67. Isoflavone urine and serum levels increased significantly ($P < 0.01$) during soy supplementation, and as expected, there was a strong correlation between the Ki67 and thymidine labeling index ($P = 0.9492$ and $P < 0.001$, respectively). However, breast lobular epithelium proliferation rate, a putative breast cancer marker, increased significantly and unexpectedly after 14 days of supplementation ($P = 0.01$).

In summary, the biological mechanisms by which phytoestrogens exert their protective effects have not been fully elucidated. However, it is tempting to speculate that high circulating levels of these compounds are achieved through dietary intake of soybean products containing their isoflavone fraction and that compounds such as genistin/daidzein and their cognate conjugates may act as weak estrogen agonists. This may result in premature maturation of mammary tissues as seen in some animal models of mammary cancer. In other settings such as human intervention trials, isoflavone treatment may result in decreased luteinizing hormone and follicle-stimulating hormone levels with corresponding decreases in estrogen, progesterone, and dehydroepiandrosterone sulfate levels. Clearly, the impact of these compounds is concentration, organ, sex, and age specific. Such issues will need further exploration before the use of isoflavone extracts can be suggested for the general population.

Phase II Studies. Upon completion of pharmacokinetic, hormonal, and biomarker studies, the National Cancer Institute has proposed short-term Phase II studies in which genistein will be administered to breast and prostate cancer patients during the period between diagnostic biopsy and definitive surgery (132). Intermediate biomarkers will be used as surrogate end points for cancer. Long-term Phase II trials may also be considered.

Discussion

Considerable epidemiological, in vitro and animal data support the notion that soybeans are chemoprotective for the development of cancer. Seventeen of 26 studies reviewed by Messina et al. (8) reported that soybean consumption reduced tumor development. Despite these reports, however, no conclusive statements could be made about the active constituents within soybeans. More recent animal studies indicate that isoflavones, protease inhibitors, and saponins are protective for both E-dependent and E-independent cancers in animal models and probably contribute additively, via different mechanisms, to the cancer chemoprotective effects seen in these systems.

Ninety-four % (16 of 17) of the animal studies reported in this review indicate that certain soy constituent(s) are protective for cancer. Of these 17 studies, 11 examined isoflavone treatment (6 genistein, 3 genistein/daidzein, 1 biochanin-A, and 1 unspecified isoflavone), 3 examined the effects of BBI, and 1 each looked at the effects of saponins, soybean meal, and soy flour.

Ten of 11 isoflavone studies (87–91, 93, 95, 97, 99, 100) reviewed here reported a positive protective effect against cancer, whereas one resulted in enhanced tumor multiplicity versus control (94). Based on the substantial amount of isoflavones used in many of these studies, it is not yet clear whether similarly efficacious concentrations can be reached in humans. Whereas most in vitro, tissue culture, and in vivo experiments have used isoflavone concentrations in excess of 10 $\mu$M, pharmacokinetic calculations that include daily dietary intake, absorption, tissue distribution, and excretion indicate that human blood isoflavone levels could probably not exceed 1–5 $\mu$M (subjects consuming soy beverage for 2 weeks had plasma genistein and daidzein levels ranging from 0.55–0.86 $\mu$M; Ref. 133). Moreover, Asian populations consuming high-soy diets have typical isoflavone levels of about 0.3 $\mu$M (134). However, because human studies indicate that soybean-derived isoflavones are readily absorbed in the body, the potential for effective soy-derived dietary supplements or enhanced soybean products exists.

All three studies (72, 73, 93) that examined the effects of the BBI in animal carcinogen models were protective for cancer. Unlike the pharmacokinetic information on isoflavones, animal studies with BBI indicate that protease inhibitor intake, at levels roughly equal to current Asian consumption (mg/kg), may be sufficient to significantly reduce adenomatous tumors of the human colon (72). Moreover, even as Asian and Seventh-Day Adventist populations consume diets rich in protease inhibitors, no known side effects have been observed (61). These calculations assume that BBI is absorbed, intact, from the human diet. However, previous studies (79, 135) indicate that protease inhibitors are not absorbed in the GI tract. Thus, although high dietary intake of protease inhibitors may result in increased levels in the colon lumen and feces, parallel increases may not be seen in internal organs such as the breast and lung (136). Presently, attempts to modify BBI seek to: (a) enhance the distribution profile by increasing absorption in the GI epithelium; (b) create lower molecular weight protease inhibitors for enhanced uptake in the bloodstream (137); and (c) attach BBI to molecules such as polysylane that are known to increase the uptake of high molecular weight compounds into cells.

Since the previous review of soy intake and cancer risk by Messina et al. (8), significant data indicating the cancer protective effects of particular soy constituents have come to light. However, discrepancies among both the animal and human data prevent any definitive claims from being made. At present, it
appears that both isoflavone phytoestrogens and BBI contribute to the chemoprotective effects seen in animals. Nonetheless, the doses required, timing and duration of therapy, and nature of the effects in humans need to be more fully developed. To this end, investigators (National Cancer Institute and others) are presently studying the effects of individual soy components in animal and human models, as well as potential methods for genetic modification of soybeans. Based on the results of future studies, it may be possible to alter soybean-based products or the soybeans themselves to achieve optimal dietary intake of chemoprotective constituents.

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Soy, its components, and cancer prevention: a review of the in vitro, animal, and human data.

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