Legumes and soybeans: overview of their nutritional profiles and health effects[1,2]

Mark J Messina

ABSTRACT Legumes play an important role in the traditional diets of many regions throughout the world. In contrast in Western countries beans tend to play only a minor dietary role despite the fact that they are low in fat and are excellent sources of protein, dietary fiber, and a variety of micronutrients and phytochemicals. Soybeans are unique among the legumes because they are a concentrated source of isoflavones. Isoflavones have weak estrogenic properties and the isoflavone genistein influences signal transduction. Soyfoods and isoflavones have received considerable attention for their potential role in preventing and treating cancer and osteoporosis. The low breast cancer mortality rates in Asian countries and the putative antiestrogenic effects of isoflavones have fueled speculation that soyfood intake reduces breast cancer risk. The available epidemiologic data are limited and only weakly supportive of this hypothesis, however, particularly for postmenopausal breast cancer. The data suggesting that soy or isoflavones may reduce the risk of prostate cancer are more encouraging. The weak estrogenic effects of isoflavones and the similarity in chemical structure between soybean isoflavones and the synthetic isoflavone ipriflavone, which was shown to increase bone mineral density in postmenopausal women, suggest that soy or isoflavones may reduce the risk of osteoporosis. Rodent studies tend to support this hypothesis, as do the limited preliminary data from humans. Given the nutrient profile and phytochemical contribution of beans, nutritionists should make a concerted effort to encourage the public to consume more beans in general and more soyfoods in particular. *Am J Clin Nutr* 1999;70(suppl):439S–50S.

KEY WORDS Legumes, soybeans, beans, phytochemicals, isoflavones, genistein, soyfoods, breast cancer, prostate cancer, cancer prevention, osteoporosis prevention, dietary fiber

INTRODUCTION

Legumes include peas, beans, lentils, peanuts, and other podded plants that are used as food. Legumes have been cultivated for thousands of years, although many of the varieties of beans and peas that are commonplace today were unknown until relatively recent times.

Legumes have played an important role in the traditional diets of many regions throughout the world. It is difficult to think of the cuisines of Asia, India, South America, the Middle East, and Mexico without picturing soybeans, lentils, black beans, chickpeas, and pinto beans, respectively. In contrast, in many Western countries beans play a less significant dietary role. In fact, bean intake has actually declined during the past century in many European countries (1).

In the United States, the availability of dry beans, peas, nuts, and soybeans combined has remained fairly constant at 7.3 kg (16 lb), 7.3 kg (16 lb), and 8.2 kg (18 lb) per person per year during the time periods 1909–1913, 1967–1969, and 1985, respectively (2). For dry edible beans specifically, the annual per capita amount available for consumption (product weight) for the years 1972, 1981, 1982, and 1992 was 2.7 kg (6.0 lb), 2.5 kg (5.4 lb), 3.0 kg (6.5 lb), and 3.4 kg (7.5 lb), respectively (3). The 1992 figure represents less than one-quarter servings of beans per person per day. Less than one-third of the adult US population eats beans during any 3-d period (3). The most popular dry bean in the United States is the pinto bean, followed by the navy, kidney, great Northern, and lima bean [annual kg per person for 1995: 1.5 (3.3 lb), 0.8 (1.7 lb), 0.3 (0.6 lb), 0.2 (0.4 lb), and 0.1 (0.2 lb), respectively] (4). In the US Department of Agriculture food guide pyramid, beans are included in the same group as nuts, meat, poultry, fish, and seeds (5). Because the recommendation is to consume $\geq$2 servings/d from this group, nonvegetarians have relatively little incentive to make beans an important part of their diets.

Beans tend to have a poor image and one that stands in stark contrast to the nutritional value they offer. Beans have been called the "poor man's meat," a metaphor which is consistent with the inverse relation between bean intake and income. For US males aged $\geq$20 y, the frequency of bean intake during a 3-d period was 36.3%, 32.3%, and 25.7% among men with incomes $<$131%, 131–350%, and $>$350% of the poverty level, respectively (3).

Given the important role of beans in populations that consume plant-based diets, it is not surprising that legume intake is higher in vegetarians than in nonvegetarians, although the data are limited (6, 7). Certainly, one would expect the consumption of beans to increase with the elimination of meat and eggs from the diet by lactovegetarians and vegans. Appropriately, the vegetarian food guide pyramid recently developed by Loma Linda University places legumes in their own group at the bottom of the pyramid (8).

[1] From Nutrition Matters, Inc, Townsend, WA.

[2] Address reprint requests to MJ Messina, Nutrition Matters, Inc, 1543 Lincoln Street, Port Townsend, WA 98368. E-mail: markm@olympus.net.

Beans have long been recognized for their protein content and more recently have been noted for their soluble-fiber content, but in general there has been relatively little research and discussion about the nutritional attributes of legumes. The glaring exception to this is the soybean, which has been investigated intensively during the past 5–10 y. This is largely because soybeans are a unique dietary source of a group of phytochemicals called isoflavones. Isoflavones are thought to exert a myriad of biological effects and it has been hypothesized that they reduce the risk of a number of chronic diseases.

This article provides an overview of the nutritional attributes of dry beans in general, and then focuses on soybeans in relation to risk of breast and prostate cancers and osteoporosis. The reader is referred to other articles in this supplement for reviews on nuts (9, 10), additional information on legumes (11), and a discussion of the effects of soy in relation to heart and kidney disease (12).

NUTRIENT COMPOSITION

Protein

The macronutrient composition of selected beans is shown in **Table 1**. The protein content of beans is generally between 20% and 30% of energy. A serving of beans (≈90 g or 1/2 cup cooked beans) provides ≈7–8 g protein or ≈15% of the recommended dietary allowance (RDA) for protein for a 70-kg adult (15). Although legumes are recognized as being high in protein, the quality of bean protein is often underestimated. This is because the protein-efficiency ratio, which is based on the growth of laboratory animals (most commonly rats), was the standard method of evaluating protein quality until recently. Rats have a methionine requirement that is ≈50% higher than that of humans (16). Consequently, because bean proteins are relatively low in sulfur amino acids (SAAs), the protein-efficiency ratios of beans are quite low (17).

However, the World Health Organization (WHO) and the US Food and Drug Administration have adopted an alternative method for evaluating protein quality called the protein digestibility corrected amino acid score (PDCAAS) (18). This method uses the amino acid score (based on the Food and Agriculture Organization estimated amino acid requirement for 2–5-y-old children) and a correction factor for digestibility to arrive at a value for protein quality. The PDCAASs of most beans are reasonably good, although their overall value is reduced somewhat by their lower digestibility (19). Some types of soy protein products have PDCAASs of close to one, the highest value possible. Some concerns have been raised about the use of the PDCAAS (20), but it certainly represents an improvement over the protein-efficiency ratio.

Ironically, the relatively low SAA content of beans may actually provide an advantage in terms of calcium retention. The reported hypercalciuric effect of protein is likely to be at least partially due to the metabolism of SAAs. The skeletal system serves as one of the main buffering systems in the body; as a result, the hydrogen ions produced from the metabolism of SAAs cause demineralization of bone and excretion of calcium in the urine (21, 22). Thus, bean protein may improve calcium retention relative to animal and grain proteins. In general, it has been estimated that every gram of protein consumed causes the loss of 1 mg Ca (23). Although this may appear to be a trivial amount, every additional milligram of calcium excreted may markedly increase dietary calcium requirements because net calcium absorption is substantially less than the average calcium absorption (≈30%) from foods. Human studies showed that the consumption of soy protein is associated with a markedly lower urinary calcium excretion compared with the consumption of similar amounts of whey protein (24) or a mixture of animal proteins (25).

With regard to bone health, the nutritional significance of substituting bean protein for animal protein depends on the relative amounts consumed. In general, this process would appear to play a minor role because legume protein, even among populations eating plant-based diets, comprises only a small percentage of total protein intake. However, the hypocalciuric effect of bean proteins may be quite important for some individuals, such as those substituting soy protein for animal protein because of its reported hypocholesterolemic effect (12) and athletes using soy protein supplements. It should be noted, however, that not all studies are in agreement about the effects of protein on calcium balance (26, 27).

Fat

Most beans are very low in fat, generally containing ≈5% of energy as fat (Table 1). The primary exceptions are chickpeas and soybeans, which contain ≈15% and 47% fat, respectively. The predominant fatty acid in beans is linoleic acid, although beans

TABLE 1
Nutrient content of selected beans (serving size is ≈90 g or ½ c boiled)[1]

Bean	Protein	Fat	Dietary fiber	Riboflavin	Folate	Ca	Zn	Fe
	% of energy		*g*	*μg*	*μg*	*mg*	*mg*	*mg*
Black	7.6, 27	0.5, 4	3.6	50	128	24	0.96	1.80
Baby lima	7.3, 25	0.4, 3	3.9	50	137	26	0.94	2.18
Chickpea	7.3, 22	2.2, 15	2.9	50	141	40	1.26	2.37
Kidney	7.7, 27	0.5, 4	3.2	50	115	25	0.95	2.60
Lentil	9.0, 31	0.4, 3	4.0	75	179	19	1.25	3.30
Navy	7.9, 24	0.5, 3	3.3	55	128	64	0.97	2.26
Soybean	14.3, 38	7.7, 47	0.9[2]	25	47	138	0.99	4.42
Pinto	7.0, 24	0.5, 3	3.4	80	147	41	0.93	2.24
Great northern	7.4, 28	0.4, 3	3.0	50	91	61	0.78	1.89
Lima	7.4, 27	0.4, 3	6.8	50	78	16	0.80	2.25

[1] From reference 13.
[2] Value represents crude fiber. From reference 14.

also contain the n−3 fatty acid, α-linolenic acid (28). However, because the overall fat content of most beans is so low, the dietary contribution of beans to α-linolenic acid intake is generally minor. As noted, soybeans are quite high in fat, and the consumption of full-fat soyfoods contributes significantly to α-linolenic acid intake. The ratio of linoleic to α-linolenic acid in soybeans is ≈7.5:1 (α-linolenic acid makes up ≈7–8% of the total fat) (28). n−3 Polyunsaturated fatty acids, especially eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are being studied for their health benefits (29–32). Adequate DHA status is particularly important for infants (33). α-Linolenic acid can be converted into EPA and EPA can be converted into DHA, although the rate of conversion of α-linolenic acid into EPA is relatively inefficient, at 5–10% (34, 35), and is inhibited by linoleic acid (34). The dietary ratio of n−6 to n−3 fatty acids among vegetarians (36) is at the high end of the rather conservative recommendations by the WHO (5:1–10:1) (37). The n−3 status of vegetarians is an issue that warrants further examination.

Micronutrients

The folate, iron, zinc, and calcium contents of selected beans are listed in Table 1. Beans are an excellent source of folate, which in addition to being an essential nutrient is thought to reduce the risk of neural tube defects (38). One serving of beans provides more than half of the current RDA for folate (15). Beans are also high in iron; 1 serving provides ≈2 mg. This compares favorably with the iron RDAs of 10 and 15 mg for adult men and premenopausal women, respectively (15). However, iron bioavailability from legumes is poor and thus their value as a source of iron is diminished (39). In acute studies, the addition of vitamin C to foods markedly increased nonheme iron absorption (40), but in longer-term studies the effects of vitamin C intake on iron absorption and status were much less pronounced (41). In general, single-meal studies overestimate the effects of both inhibitors and enhancers of nonheme iron absorption (42).

In contrast to iron bioavailability, zinc bioavailability from legumes is relatively good at ≈25% (43). Also, many beans are good sources of calcium, providing on average ≈50 mg Ca/serving, although there is quite a bit of variation among the legumes. Calcium bioavailability from beans in general is ≈20%, which is lower than that from milk and green leafy vegetables but is still reasonably good (44). Calcium bioavailability from soybeans and soyfoods is quite good—essentially equivalent to calcium bioavailability from milk—despite the fact that soybeans are high in phytate and oxalate (45).

Fiber and the glycemic index

Beans are an excellent source of dietary fiber; 1 serving provides 2–4 g of a mix of soluble and insoluble fiber (46). High-fiber, high-bean diets were shown to lower serum cholesterol in hypercholesterolemic individuals (47). In addition, beans have very low glycemic indexes (48, 49). This has been attributed to many factors including their fiber (50), tannin (51), and phytic acid contents (52). Although neither the American Diabetes Association nor the American Dietetic Association endorse the glycemic index as a tool for constructing diets for individuals with diabetes (53), research published during the past decade makes a persuasive argument that the glycemic index of foods is one factor affecting the overall quality of the diet (54). In support of this statement are findings from a prospective study showing that women who consumed diets with a high glycemic index were ≈40% more likely to develop diabetes than those consuming low-glycemic-index diets, even after controlling for several diabetes risk factors (55). Thus, beans may be a particularly important food for individuals with diabetes and those with an elevated risk of developing diabetes.

Nonnutritive components

Beans contain several components that traditionally have been considered to be antinutrients, such as trypsin inhibitors, phytate (inositol hexaphosphate), oligosaccharides, and saponins. More recent information suggests, however, that the antinutrient label may be an oversimplification, especially in the case of oligosaccharides and saponins. Trypsin inhibitors from beans can certainly interfere with protein digestion, and in some species of animals do cause pancreatic enlargement and enhance chemically induced pancreatic tumors (56). However, boiling dry beans generally reduces the trypsin inhibitor content by 80–90% (57) and there is little reason to think that the amount of trypsin inhibitors obtained by eating commonly consumed beans would exert any adverse effects in humans (58). In contrast to the trypsin inhibitor, the trypsin and chymotrypsin inhibitor (Bowman-Birk inhibitor) found in beans, especially soybeans, has been studied as an anticancer agent (59).

As noted above, phytate is thought to contribute to the poor mineral bioavailability of beans. On average, the phytate concentration in beans is between 1% and 2% (60, 61). Although the effect of phytate in reducing mineral bioavailability in plant foods is an important consideration, it has also been postulated that phytic acid may play a role in reducing cancer risk, possibly because of its antioxidant effects (62). Specifically, it has been suggested that phytic acid may lower the risk of colon cancer (63) and perhaps breast cancer (64).

More than 40 y ago, diets containing beans were first shown to markedly increase flatulence (65). In 1970, it was reported that the oligosaccharides in beans were responsible for gas production (66). The oligosaccharide content of dry beans is ≈25–50 mg/g (67, 68). Because there is no α-galactosidase in the human intestinal mucosa to cleave the α-(1–6) galactose linkage present in galactoside-containing oligosaccharides, such as raffinose and stachyose, these oligosaccharides pass into the large intestine where bacteria metabolize them and form large amounts of carbon dioxide, hydrogen, and sometimes methane. Because of the discomfort and social embarrassment associated with flatulence, some people opt to avoid beans entirely.

Commercial products such as Beano (AkPharma Inc, Pleasantville, NJ), a digestive aid that contains α-galactosidase, are available so that individuals can eat beans without discomfort. Additionally, it is possible to remove substantial amounts of oligosaccharides and to markedly reduce flatulence by changing the water in which beans are boiled one or more times (69). However, there may be some beneficial effects associated with oligosaccharide consumption. The oligosaccharides, because of their growth-promoting effect on bifidobacteria, have been hypothesized to promote the health of the colon, increase longevity, and decrease colon cancer risk (70–72). In fact, for these reasons researchers in Japan have actually suggested that soybean oligosaccharides be used as a substitute for common table sugar (73). For a more detailed discussion of oligosaccharides, *see* Slavin et al in this supplement (74).

Saponins are glycosides composed of a lipid-soluble aglycone that consists of either a sterol or, more commonly, a triterpenoid

structure attached to water-soluble sugar residues that differ in their type and amount. The major sources of dietary saponins are legumes, and many types of saponins can be present in the same bean. Saponins are very poorly absorbed. Most saponins form insoluble complexes with 3-β-hydroxysteroids and are known to interact with and form large, mixed micelles with bile acids and cholesterol. Although saponins were shown to lower cholesterol in some animal species, the hypocholesterolemic effects of saponins in humans are more speculative (75). Saponins may have anticancer properties, as suggested by a recent rodent study that found that a saponin-containing diet (3% by wt) inhibited by about two-thirds the development of azoxymethane-induced preneoplastic lesions in the colon (76). However, given that human intake of saponins is generally ≤200–300 mg/d whereas total food intake is ≈500 g (dry weight), it is not clear to what extent these results in rodents are relevant to humans (7).

Isoflavones make up another group of phytochemicals found in beans, but for practical purposes the soybean is the only nutritionally relevant source of these compounds. Soybeans and soy products contain ≈1–3 mg isoflavones/g protein; 1 serving of traditional soyfoods provides ≈25–40 mg isoflavones (77, 78). Isoflavones have received considerable attention in recent years. They are being studied for their potential role in the prevention and treatment of a number of chronic diseases including certain forms of cancer, osteoporosis, and heart disease, and also for their ability to relieve menopausal symptoms.

Soybean isoflavones

Isoflavones are a subclass of the more ubiquitous flavonoids. The basic structural feature of flavonoid compounds is the flavone nucleus, which is composed of 2 benzene rings (A and B) linked through a heterocyclic pyrane C ring (**Figure 1**). The position of the benzenoid B ring is the basis for dividing the flavonoid class into flavonoids (2-position) and isoflavonoids (3-position). The primary isoflavones in soybeans are genistein (4′,5,7-trihydroxyisoflavone) and daidzein (4′,7-dihydroxyisoflavone) and their respective β-glycosides, genistin and daidzin (sugars are attached at the 7 position of the A ring). Much lower amounts of glycitein (7,4′-dihydroxy-6-methoxyisoflavone) and its glycoside, glycitin, are present in soybeans (79). In nonfermented soyfoods, the isoflavones appear mostly as the conjugate, whereas in fermented soy products such as miso, the aglycones dominate (78).

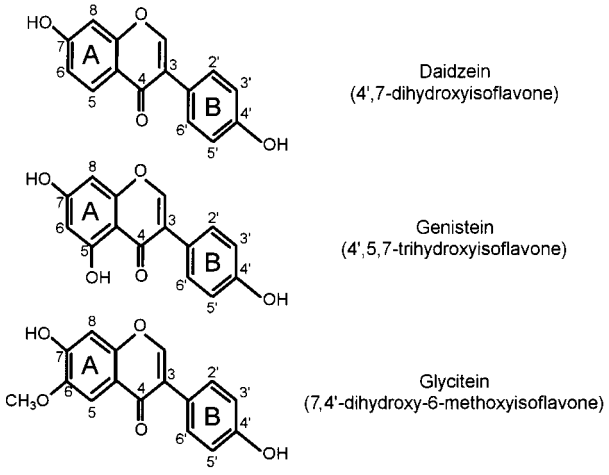

FIGURE 1. Structures of the primary isoflavones in soybeans.

In addition to the isoflavones found in soybeans, the intestinal microflora can convert daidzein into several different products, including the isoflavonoids equol (7-hydroxyisoflavan), dihydrodaidzein, and *O*-desmethylangolensin (80). However, because of differences in intestinal microflora, equol production occurs in only ≈1 out of every 3 individuals consuming soyfoods (81, 82). It has been proposed that in humans, genistein is metabolized to dihydrogenistein and 6′-hydroxy-*O*-desmethylangolensin (80).

Estrogenic and antiestrogenic activity

Initial interest in the beneficial effects of isoflavones focused on their estrogenic activity and their possible use in the animal feed industry as growth promoters (83). On a molar basis relative to physiologic estrogens, isoflavones are quite weak according to both in vitro and in vivo assays, possessing between 1×10^{-4} and 1×10^{-3} the activity of 17β-estradiol (84–90). Despite their relatively low potency, isoflavones are likely to exert physiologic effects because it has been shown that in people who consume soyfoods, serum concentrations of isoflavones are several orders of magnitude higher than those of physiologic estrogens. Studies have found that, in response to the consumption of soyfoods, blood isoflavone concentrations can reach the low micromolar range (≤6 μmol/L) (91), although concentrations in free-living Japanese men are generally in the high nanomolar range (300–400 nmol/L) (92).

Although isoflavones are weak estrogens, Folman and Pope (84) showed >30 y ago that in female mice genistein injected subcutaneously inhibited estrone stimulation of uterine growth; thus, the authors concluded that genistein could function as an antiestrogen. The prevailing hypothesis has been that isoflavones exert antiestrogenic effects when placed in a high-estrogen environment, such as exists in premenopausal women, and estrogenic effects when in a low-estrogen environment, such as exists in postmenopausal women. This hypothesis has some support; for example, Mäkela et al (93) found that in ovariectomized mice not given the synthetic estrogen diethylstilbestrol (DES), uterine weight increased in those fed soy compared with control animals (0.87 and 0.76 mg/g body wt, respectively; $P < 0.001$). In mice given DES, uterine weight decreased in those fed soy compared with control animals (1.01 and 1.49 mg/g body wt, respectively; $P < 0.001$).

In addition to competing with endogenous estrogens for binding to the estrogen receptor, there are several potential mechanisms by which the isoflavones may exert antiestrogenic effects (reviewed in 94). However, there are conflicting results about when isoflavones and soy exert hormonal effects and whether these effects are estrogenic or antiestrogenic in nature (95–106). This should not be surprising given recent insights into the intricacy of the ligand-estrogen receptor binding complex (reviewed in 107) and the identification of a novel, second estrogen receptor, β, to which isoflavones bind (108). Particularly germane to this issue, however, are the findings of 2 human studies suggesting that soy consumption exerts estrogenic effects on breast tissue. Epidemiologic research by Wrensch et al (109) showed that breast-nipple-aspirate fluid is a biomarker for breast cancer risk. Women who secrete fluid are at increased risk compared with nonsecretors, and women who secrete fluid containing cells with abnormal cytology (eg, hyperplastic cells) are also at increased risk. In a 9-mo study by this group, contrary to expectations, breast fluid secretion in

both premenopausal and postmenopausal women taking hormone replacement therapy increased in response to soy consumption, as did the number of atypical cells in the breast fluid (110). However, this was a pilot study that did not include a control group.

In a recent study of premenopausal women by McMichael-Phillips et al (111), the rate of DNA synthesis by breast cells taken from biopsies of normal breast tissue from women with benign or malignant breast disease was enhanced by 2 wk of soy feeding. Although the clinical implications of this study and the study by Petrakis et al (110) are a matter of debate, when the in vitro, animal, and human data are considered it is difficult to conclude that soy or isoflavones are necessarily antiestrogenic in premenopausal women.

Effects of soy and isoflavones on cancer risk

Data regarding the relation between soy intake and cancer risk, including in vitro, animal, and epidemiologic results, were reviewed by Messina et al (112). On the basis of this review, it is clear that the data are insufficient to conclude that soy consumption is protective, and yet the data certainly warrant continued investigation of this relation. Besides isoflavones, there are a number of phytochemicals in soybeans with demonstrated anticarcinogenic activity; these include phytosterols, phytates, saponins, protease inhibitors, and a variety of phenolic acids (113). However, most of the data point toward the isoflavones as being responsible for the hypothesized anticancer effects of soy.

Daidzein, one of the 2 primary isoflavones in soybeans, exhibits anticancer effects; eg, it inhibited the growth of HL-60 cells implanted in the subrenal capsules of mice (114). However, genistein has attracted most of the interest. There are literally hundreds of in vitro studies showing that genistein inhibits the growth of a wide range of both hormone-dependent and hormone-independent cancer cells with an IC_{50} between ≈5 and 40 μM (2–10 μg/mL), including breast (115–121), prostate (122–124), colon (125, 126), and skin (127) cells (reviewed in 94, 128, 129). Also, in vitro, genistein inhibits the metastatic activity of both breast (130) and prostate (131) cancer cells independent of the effects on cell growth.

Although the antioxidant properties of genistein may contribute to the anticancer effects observed in vitro (132), it is more likely that these effects are due to the inhibitory actions of genistein on several enzymes involved in signal transduction, including tyrosine protein kinases (133), MAP kinase (134), and ribosomal S6 kinase (135). Genistein also inhibits the activity of DNA topoisomerase II (136) and Peterson et al (137) recently reported that genistein increased the in vitro concentrations of transforming growth factor β (TGFβ). This last finding may be particularly important given the role that TGFβ may have in inhibiting the growth of cancer cells (138–140). Although there are in vitro, animal, and epidemiologic data supporting a protective role of soy or isoflavones against several forms of cancer, this review will consider only breast and prostate cancers because most of the focus has been on these 2 cancers.

Breast cancer

Research on the relation between soy intake and cancer risk initially focused primarily on cancer of the breast. In large part, interest in this relation was due to the relatively low breast cancer mortality rates in Asian countries where soyfoods are commonly consumed. In Japan for example, the breast cancer mortality rate is only about one-quarter of that of the United States (141). In addition to the low breast cancer mortality rates in Asia, 2 other early observations provided a basis for the hypothesis that soy intake decreases breast cancer risk: *1*) the potential antiestrogenic effects of the soybean isoflavones as discussed above, and *2*) the reduced number of 7,12-dimethylbenz(a)anthracene–induced mammary tumors observed in rats fed a diet containing soy (142). Since this hypothesis was initially proposed, several epidemiologic studies have examined the relation between soy intake and breast cancer risk.

In 1991, a case-control study conducted by Lee et al (143) in Singapore (n = 200 case subjects and 420 control subjects) found that regular consumption of soyfoods was associated with a marked decrease in breast cancer risk in premenopausal women (odds ratio: 0.39; 95% CI for the highest fifth compared with the lowest fifth of intake of total soy products: 0.19, 0.77; $P < 0.02$) but not postmenopausal women. A Japanese case-control study (n = 1186 case subjects and 23 163 control subjects) also found that tofu intake (≥3 times/wk compared with <3 times/wk) was associated with decreased risk of breast cancer in premenopausal women (odds ratio: 0.81; 95% CI: 0.65, 0.99; $P < 0.05$), but again, soy intake was not protective against postmenopausal breast cancer (144). In contrast to these studies, a case-control study involving 2 different locations in China [Shanghai (n = 534 case subjects and 534 control subjects) and Tianjin (n = 300 case subjects and 300 control subjects)] failed to find an association between soyfood intake and breast cancer risk in either pre- or postmenopausal women (145).

The only case-control study (n = 596 case subjects and 958 control subjects) conducted thus far in the United States to examine the relation between soy intake and breast cancer risk found that tofu consumption was protective in both premenopausal (adjusted odds ratio: 0.67) and postmenopausal (adjusted odds ratio: 0.70) Asian women (146). However, the overall intake of tofu among the subjects in this study was relatively low; the highest quartile of intake included women who consumed tofu as infrequently as 55 times per year. Also, the protective effect was primarily in Asian women born in Asia who migrated to the West and not in Asian Americans born in the United States (146). One interpretation of these findings is that tofu intake per se is not protective but rather that it is simply reflective of some protective lifestyle common to women of Asian ancestry born in Asia but not those born in the United States. Alternatively, the anticancer effects of tofu may be negated by a lifestyle common to women of Asian ancestry born in the United States but not those born in Asia. Finally, in the Iowa Women's Study, a prospective study involving >34 000 women, it was found after 8 y of follow-up that tofu intake was associated with a modest decrease in postmenopausal breast cancer risk (adjusted relative risk for any consumption compared with no consumption: 0.76), although this was not a statistically significant effect ($P < 0.22$) (147). Not unexpectedly, only 2.9% of the cohort reported eating any tofu.

Overall, the epidemiologic data are inconclusive. There is relatively little epidemiologic support for the notion that soy intake is associated with a decreased risk of postmenopausal breast cancer. However, there are some limited data, albeit inconsistent, suggesting that soy intake is associated with a decreased risk of premenopausal breast cancer.

As noted previously, genistein has been shown to inhibit the growth of both estrogen-dependent and estrogen-independent breast cancer cells in vitro, but it is not clear that cellular concentrations of genistein in vivo would reach the in vitro concen-

trations required to inhibit breast cancer–cell growth. It should be noted, however, that Peterson and Barnes (148) found that genistein inhibits the serum and epidermal growth factor–stimulated growth of normal human mammary epithelial cells with IC_{50} values 11–15-fold lower than those for human transformed breast epithelial cells. Thus, soy intake may help to prevent the initiation of cancer cells, rather than inhibiting the growth of existing cancer cells.

In a study by Constantinou et al (149), neither genistein nor daidzein (injected intraperitoneally) inhibited *N*-methyl-*N*-nitrosourea–induced mammary tumor incidence in Sprague-Dawley rats, although both isoflavones had a moderate but not statistically significant effect on tumor multiplicity (6.7 compared with 4.9 tumors/rat). Because synergistic effects between genistein and daidzein have been noted in vitro, it would be of interest to examine their combined effects in vivo (150, 151). Of course there is also the possibility that other components of soybeans, individually or in conjunction with isoflavones, are responsible for the hypothesized anticancer effects of soyfoods.

It is apparent from the human studies by Wrensch et al (109), McMichael-Phillips et al (111), and Cassidy et al (103, 104) that soy or isoflavones have the potential to exert physiologic effects theoretically related to breast cancer risk. In particular, Cassidy et al (103) found that the consumption of soy, specifically isoflavone-rich soy (104), extends the length of the follicular phase and decreases serum follicle-stimulating hormone and luteinizing hormone concentrations. It is certainly not possible to conclude at this time that consumption of soyfoods in adulthood is a factor that contributes to the low breast cancer mortality rates among Japanese and Asian women, although this hypothesis still warrants rigorous investigation.

Finally, there are provocative data from Brown and Lamartiniere (152), Lamartiniere et al (153), and Murrill et al (154) suggesting that the early consumption of soyfoods by young girls may reduce breast cancer development later in life. This research group has shown that early exposure (during the neonatal or prepubertal period of life) to genistein (subcutaneous administration) inhibits the development of dimethylbenz(a)anthracene-induced mammary tumors in rodents and increases the latency period (152–154). These findings offer a potential explanation for the findings of Wu et al (146). Perhaps Asian women born in Asia are exposed to tofu at an earlier age than Asians born in the West. Certainly, the work of this group provides the basis for an intriguing line of investigation, especially because recent research indicates that early dietary exposure to genistein is also effective in retarding later development of mammary cancer.

Prostate cancer

As is the case for breast cancer, prostate cancer mortality rates vary markedly among countries. An interesting observation related to the occurrence of prostate cancer is that rates of clinical prostate cancer vary much more than rates of latent prostate cancer. For example, the US incidence of clinical prostate cancer among whites is 10–15-fold higher than the Japanese rate, whereas the overall incidence of latent prostate cancer is only ≈50% higher (155). This suggests that in some populations, such as the Japanese, the growth of prostate tumors is slower, the onset of prostate tumors occurs later in life, or both. Delaying the appearance of clinical prostate tumors by even a few years could have a marked impact on mortality because prostate cancer typically occurs in older men. There is speculation that the intake of soyfoods may be a factor contributing to the low prostate cancer mortality rate in Japan, although the data in support of this hypothesis, while intriguing, are limited.

Genistein inhibits the growth of both androgen-dependent and androgen-independent prostate cancer cells in vitro (122, 123). Genistein also inhibits the metastatic potential of prostate cancer cells independent of cell growth inhibition, an effect that is associated with a decrease in the tyrosine phosphorylation of an unidentified molecular species (131).

In addition to the effects of genistein on signal transduction that were noted previously, there are other mechanisms by which genistein or isoflavones could reduce prostate cancer risk. For example, even though the precise role of estrogen in prostate cancer is not well defined, the potential estrogenic effects of isoflavones may be protective because estrogens have been used successfully as a form of hormone therapy for metastatic prostate cancer (156). Also, some data indicate that genistein inhibits the activity of 5-α-reductase in genital skin fibroblasts and benign hyperplastic prostate tissue (150). This enzyme converts testosterone into the more active form of androgen, dihydrotestosterone, which stimulates the growth of prostate tissue. Ross et al (157) showed that biomarkers of 5-α-reductase activity are higher in white and black men compared with Japanese men. The in vitro data from Evans et al (150) are consistent with findings from Lu et al (158), who reported that after 1 mo of soymilk consumption (36 oz/d), serum concentrations of 3α,17β-androstanediol glucuronide, a metabolite of dihydrotestosterone, were significantly reduced.

Until recently, there were few animal studies related to soy and prostate cancer. In 1995, Mäkela et al (93) reported that after feeding mice a diet containing soy for 9 mo, the incidence of prostatic dysplasia, which may viewed as a preneoplastic prostate lesion, was markedly reduced compared with the incidence in mice fed a diet not containing soy (30% and 80%, respectively). At 12 mo, however, there was much less difference between the 2 groups (64% compared with 86%). These findings are consistent with the epidemiologic data noted above and also with the results of a study of MNU-induced prostate tumors in Lobund-Wistar rats (159). Rats fed a diet containing soy with a low amount of isoflavones had a shorter latency period [7.3 mo for pre-MNU group and 9.3 mo for post-MNU group] than those fed a diet containing soy high in isoflavones [10 mo for pre-MNU group and 10.6 mo for post-MNU group] (159).

Three studies examined the effect of soy or genistein on tumor development in rats implanted with prostate cancer cells (123, 160, 161). Zhang et al (160) found that in rats fed a diet containing soy flour (33% by weight) and implanted with Dunning R3327 PAP tumors, tumor growth was significantly retarded at 16 wk compared with animals fed the control diet. Schleicher et al (161) found that genistein (50 mg/kg body wt) given under the skin in the dorsal scapular area every 12 h starting at the time of tumor cell transplantation inhibited the development of prostate tumors in rats implanted with prostate carcinoma cells. Rats given genistein developed fewer tumors and fewer invasive tumors, and no genistein-treated animals developed lung metastases.

Insight into a possible mechanism for the inhibitory effects of genistein came from Dalu et al (162), who found that in Lobund-Wistar rats, dietary genistein (1 mg genistein/g diet) reduced the weight of the dorsolateral and ventral prostates and inhibited the expression of tyrosine-phosphorylated proteins. This study was the first to show that in vivo, genistein inhibits a key cellular path-

way. Related to this finding are those of Geller et al (163), who found that genistein (at concentrations of 1–15 μg/mL) inhibited the incorporation of 3H-thymidine (a measure of tissue growth) in cultured benign prostatic hypertrophy tissue by 44–86% in a dose-dependent fashion.

In contrast to the favorable results discussed above, Naik et al (123) found that although genistein inhibited prostate cancer cell growth in vitro, when Copenhagen rats were injected in the right flank with the metastatic MAT-Lylu prostate cancer line, oral doses of genistein (0.07, 0.143, and 0.285 mg/d) failed to inhibit the development of prostate tumors. These doses more closely approximated human dietary intake than the amounts used by Schleicher et al (161) and Dalu et al (162). Higher doses of genistein (0.143, 0.285, and 0.428 mg/kg) injected by the intraperitoneal route also had little effect on tumor growth (123).

Not surprisingly, there are limited human data available for use in evaluating the soy–prostate cancer hypothesis, although a prospective study by Severson et al (164) found that consumption of tofu was associated with a markedly reduced risk of prostate cancer (age-adjusted relative risk: 0.35 for subjects who ate tofu ≥5 times/wk compared with those who ate tofu ≤1 time/wk). However, this difference did not quite reach statistical significance ($P < 0.054$) and the number of men with tumors in each of the tertiles was small (164). Of potential relevance to the effects of isoflavones on prostate cancer risk is the finding that isoflavones appear in the prostatic fluid, and that concentrations are highest in men from soyfood-consuming countries (165). Furthermore, relative to plasma concentrations, isoflavones are concentrated several-fold in the prostatic fluid. Interestingly, a recent case study reported significant apoptosis in a prostatic specimen from a man with adenocarcinoma who had taken isoflavones (160 mg/d) derived from red clover 1 wk before surgery. The red clover extract contains both genistein and daidzein as well as the methylated isoflavones, biochanin-A and formononetin, from which genistein and daidzein, respectively, are derived (166).

Cancer treatment

There has been some speculation that soy or isoflavones could be used in the treatment of existing tumors, either alone or in conjunction with conventional chemotherapeutic agents. Support for this speculation comes from work by Fotsis et al (167) who found that at high concentrations (IC_{50}, 150 μmol), genistein inhibited the ability of bovine microvascular cells to invade collagen gels and generate capillary-like structures when stimulated by basic fibroblast growth factor. Development of antiangiogenesis agents is a highly promising area of cancer treatment because inhibiting the tumor-stimulated growth of new blood vessels prevents tumors from becoming larger than 1–2 mm. Tumors limited to this size are clinically insignificant (168). The concentration of genistein required to inhibit angiogenesis in vitro, as reported initially (167), is certainly much higher than the genistein concentration likely to be achieved in vivo. However, it has since been reported that a much lower genistein concentration is required for angiogenesis inhibition in vitro (IC_{50}, 8 μmol) (94), and that the initial higher concentration was a result of incomplete solubilization of genistein in the media.

There is some preliminary support from in vivo research for the antiangiogenic potential of genistein. In a small study of patients with hereditary hemorrhagic telangiectasia, soy intake led to a marked reduction in nosebleeds and gastrointestinal bleeding (JR Korzenik, S Barnes, unpublished observations, 1996). A larger, follow-up study is currently underway. Interestingly, the genes in which hereditary hemorrhagic telangiectasia mutations have been mapped thus far all encode for proteins that are involved in TGFβ signaling (169) and as noted previously, Peterson et al showed that in vitro, genistein increases TGFβ levels (137).

Soy and bone health

The similarity in structure between the isoflavones and estrogen and the findings that isoflavones possess weak estrogenic properties as shown by various experimental models provided the initial basis for speculation that isoflavones may promote bone health. Speculation about the potential benefits of isoflavones was also fueled by the similarity in chemical structure between the soybean isoflavones and the synthetic isoflavone, 7-isopropoxyisoflavone (ipriflavone), which was shown to increase bone mass in postmenopausal women (170, 171).

Interestingly, for ipriflavone to be maximally effective it requires metabolism, and one of the metabolites of ipriflavone is the soybean isoflavone daidzein (166). The usual dose of ipriflavone is between 600 and 1200 mg/d. Reportedly, daidzein comprises 10% of the metabolic products of ipriflavone (171), although it is not clear to what extent daidzein is actually responsible for the effects of ipriflavone on bone resorption; it appears to be one of several metabolites able to inhibit osteoclast activity in vitro (172).

The lower rate of hip fracture among Japanese women in comparison to US women (173, 174) is often cited as providing support for a protective effect of isoflavones, but this line of reasoning appears to be without merit. The bone density of Japanese women is similar to or lower than that of US women, whose hip fracture rate is twice as high (175–177). Furthermore, the Japanese vertebral fracture rate is actually much higher than that of US women (176). The low Japanese hip fracture rate is thought to be due at least in part to anatomical differences between white and Japanese women, such as the shorter hip axis length of Japanese women (178), and perhaps also to other factors such as a lower tendency to fall (179).

Until recently there were no direct data indicating that the soybean isoflavones affect bone density. In 1995, Anderson et al (180) reported that genistein exhibited a biphasic effect on bone in 2 different models of ovariectomized rats, young growing rats and lactating rats, both of which were fed low-calcium diets. These studies used 3 different doses of genistein: 1.0, 3.2, and 10 mg/d. After 2 wk of treatment for the young growing rats and 5 wk of treatment for the lactating rats, genistein at the lowest dose helped to prevent ovariectomy-induced, bone-related changes to an extent similar to the effects of conjugated equine estrogens (5 μg/d).

In 1996, Arjmandi et al (98) studied the effects of soy protein on bone loss due to ovariectomy. Sprague-Dawley rats were divided into 4 groups: *1*) sham operated, *2*) ovariectomized plus casein, *3*) ovariectomized plus soy (0.227 g/g diet, isoflavone content not indicated), and *4*) ovariectomized plus estrogen. The bone density of the right femur was highest in the group given estrogen and lowest in the ovariectomized animals fed casein. The bone density of the soy group was significantly lower than that of the estrogen and sham groups, but significantly higher than that of the ovariectomized group fed casein. Bone density of the fourth lumbar vertebra of the soy group was equal to that of the estrogen group and significantly higher than that of both the casein and sham groups. This suggests that soy is more protective of trabecular bone than cortical bone. Similar conclusions

were reached by Anderson et al (180). In a follow-up study by Arjmandi et al (181), in which a similar experimental model as described above (98) was used, a soy product low in isoflavones did not affect bone density favorably but a soy product high in isoflavones did, clearly suggesting that the isoflavones are responsible for these beneficial effects of soy.

Two other rat studies suggest that genistein in particular affects bone density (182, 183). Blair et al (182) fed ovariectomized rats an AIN-76 diet (ICN Pharmaceuticals Inc, Cleveland) or the same diet containing 30 μmol genistein/d for 4 wk. The dry femoral mass of the animals fed genistein was 12% higher ($P < 0.05$) than that of the controls. In a study by Fanti et al (183), after 21 d of treatment with genistein in ovariectomized rats, 5 and 25 μg genistein/g body wt injected subcutaneously significantly reduced ovariectomized tibial bone mineral loss; however, 1 μg genistein/g body wt was ineffective.

In contrast to the favorable effects observed in rat studies (98, 180–183), Jayo et al (100) found that in ovariectomized cynomogulus monkeys, feeding diets containing soy with or without isoflavones for 23 mo did not retard the loss of lumbar spine bone mineral content, whereas monkeys given conjugated equine estrogens had an increase in bone mineral content during this period. Also, in rats a diet containing an amount of soy that retarded ovariectomy-induced bone loss when administered immediately after surgery had no effect when diet administration was delayed until 35 d after ovariectomy (184). The implications of this finding may be quite significant given that recent research suggests that estrogen can exert favorable effects on bone density even when administration is delayed for many years after menopause (185).

Two human studies that examined the effects of soy consumption on bone mineral loss in postmenopausal women have been reported thus far (186, 187). In both studies, soy was associated with favorable effects on bone density or content; however, the results of these studies should be considered preliminary. Potter et al (186) reported that after 6 mo of treatment, lumbar spine bone mineral density increased significantly compared with baseline values in postmenopausal women who consumed 40 g soy protein containing 2.25 mg isoflavones/g protein daily, whereas bone density remained essentially the same in women who consumed the same amount of soy protein but containing only 1.39 mg isoflavones/g protein. Women who consumed 40 g of a mixture of casein and nonfat dry milk lost bone mineral density (186). Dalais et al (187) found that early postmenopausal women had a 5% increase in bone mineral content compared with baseline values after only 3 mo of consuming soy flour. Not only does the magnitude of this increase raise questions about these findings, but the control subjects, who were fed wheat protein, also experienced an increase in bone mineral content which is surprising given that all the subjects were early postmenopausal women (187).

Some insight has been gained into the possible mechanism(s) underlying the effect of isoflavones on bone health in rats. There are data suggesting that isoflavones may both stimulate and inhibit bone formation. For example, Fanti et al (183) found that genistein increased osteoblast numbers and serum osteocalcin concentrations, but had no effect on osteoclast numbers. Conversely, Blair et al (182) studied the effects of genistein on avian osteoclasts in vitro and found that osteoclast protein synthesis was significantly inhibited, an effect that might be due to the inhibitory effects of genistein on tyrosine phosphorylation. It is also worth noting that estrogen and tamoxifen, both of which inhibit bone resorption, cause osteoclast apoptosis, an effect that is inhibited in vitro by the addition of antibodies to TGFβ (188). As noted previously, genistein was shown to increase TGFβ in vitro, and thus an effect of genistein on bone resorption may be mediated by this cytokine.

The relation between isoflavones and bone health is provocative. Thus far, no long-term human studies have examined the effects of either soy or isoflavones on bone density or even markers of bone formation and resorption, let alone fracture risk. Consequently, although the effect of soy and isoflavones on bone health constitutes an exciting area of research, no firm conclusions can be reached at this time. Fortunately, because of the number of studies underway, it is likely that a much better understanding of this issue will be obtained within a relatively short period of time.

SUMMARY AND CONCLUSIONS

Legumes have traditionally been an important part of the diets of many cultures throughout the world. In contrast, in developed countries beans currently have only a minor dietary role. The nutritional profile of beans shows that they have much to offer; beans are high in protein, low in saturated fat, and high in complex carbohydrates and fiber. Beans are also a good source of several micronutrients and phytochemicals. Soybeans are unique among the legumes because they are a concentrated source of isoflavones. It has been hypothesized that isoflavones reduce the risk of cancer, heart disease, and osteoporosis, and also help relieve menopausal symptoms. Although there is much to learn about the effects of isoflavones on chronic disease risk, this area of research holds considerable potential. Given the nutrient profile and phytochemical contribution of legumes, nutritionists should make a concerted effort to encourage the public to consume more beans in general and more soyfoods in particular.

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