

Insights Gained from 20 Years of Soy Research^{1,2}

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Abstract

Soyfoods have long been recognized for their high-protein and low-saturated fat content, but over the past 20 y an impressive amount of soy-related research has evaluated the role of these foods in reducing chronic disease risk. Much of this research has been undertaken because the soybean is essentially a unique dietary source of isoflavones, a group of chemicals classified as phytoestrogens. The estrogen-like properties of isoflavones have also raised concern, however, that soyfoods might exert adverse effects in some individuals. There is intriguing animal and epidemiologic evidence indicating that modest amounts of soy consumed during childhood and/or adolescence reduces breast cancer risk. Evidence also suggests that soy reduces prostate cancer risk and inhibits prostate tumor metastasis, but additional clinical support for the chemopreventive effects of soyfoods is needed. Soy protein is modestly hypocholesterolemic and there is suggestive epidemiologic evidence that soyfoods lower risk of coronary heart disease (CHD) independent of effects on cholesterol. In clinical studies, soy favorably affects multiple CHD risk factors; however, with the exception of improved endothelial function, the data are too limited and/or inconsistent to allow definitive conclusions to be made. In regard to bone health, although recent clinical data have not supported the skeletal benefits of isoflavones, 2 large prospective epidemiologic studies found soy intake is associated with marked reductions in fracture risk. Soybean isoflavones also modestly alleviate hot flashes in menopausal women. Finally, other than allergic reactions, there is almost no credible evidence to suggest traditional soyfoods exert clinically relevant adverse effects in healthy individuals when consumed in amounts consistent with Asian intake. J. Nutr. doi: 10.3945/jn.110.124107.

Introduction

A mere 2 decades ago, unless their client or patient was a vegetarian, health professionals had little reason to know much about the health attributes of soyfoods, perhaps other than that they were good sources of protein. No longer is this the case. The

popularity of foods made from the soybean, which have been consumed for centuries in many Asian countries, has increased markedly in the United States and other Western countries. This increased popularity has occurred largely because of consumer belief that soyfoods may confer health benefits independent of their nutrient content. Soyfoods also appeal to those interested in eating a plant-based diet for ethical and environmental reasons, the latter of which is gaining scientific support (1).

Nevertheless, the role of soyfoods in an overall healthy diet has become somewhat of a confusing and contentious issue in recent years. Understanding and interpreting the enormous amount of soy research conducted is challenging, because it requires understanding the strengths and weaknesses of a wide variety of experimental models and designs. The extent to which inconsistencies in the literature result from soy product-specific effects is a matter of much discussion (2). These products range from isolated soybean constituents such as isoflavones to “whole soyfoods,” although there is no uniform definition of the latter.

Most soy research has focused on isoflavones and soy protein. However, not only may other soybean components exert important health effects, but there is the potential for interactions among the various components to result in outcomes difficult to predict from knowledge of the individual soybean components (3). Clearly, however, in some cases, the health effects of soyfoods are ascribed to specific components.

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The perceived inconsistency between findings from Asian epidemiologic studies, which are generally viewed as supportive of health benefits, and the clinical studies, which are viewed as being less so, is commonly cited as an example of soy products differentially affecting health outcomes. The epidemiologic data are based on the intake of traditional soyfoods, such as tofu, miso, and soymilk, whereas the intervention products almost exclusively have been isolated soy protein (ISP;³ by definition ISP is $\geq 90\%$ protein) and soy isoflavone supplements. However, even if one accepts that a discrepancy between the epidemiologic and clinical datasets exists, there are explanations aside from differences in the chemical composition of the soy products in question that might account for this inconsistency. These include the timing and duration of exposure and ethnic differences in response to soy. There is also the possibility that the Asian epidemiologic studies are simply identifying a “healthy user effect” and not a direct effect of soy intake.

Soyfoods and the Dietary Guidelines

That the soybean (*Glycine max*) is a legume can be overlooked, because for the most part it is not consumed directly as the bean, as are most legumes, but rather as already noted, in the form of foods such as tofu, soymilk, tempeh, and miso. These foods have little obvious physical resemblance to the native bean. Even edamame or green (immature) soybeans look and taste more like a vegetable than a legume. Soy protein products such as soy protein concentrate, ISP, and soy flour are even less likely to conjure up images of beans.

Legumes are an underutilized food source in the United States despite their being included in the Dietary Guidelines in both the meat and bean group and the vegetable group. Soyfoods represent a convenient way to meet the legume recommendation and for this reason alone their consumption can be encouraged. The Dietary Guidelines recommend consuming 3 cups (6 servings or ~ 540 g) of legumes per week, but few Americans meet that goal. Data from the NHANES 1999–2002 revealed that only 7.9% of the adult population consumed beans, peas, or lentils on any given day (4). Europeans (5) and North Americans (6) typically get only a fraction of their protein from legumes, which contrasts with the situation in Asian countries, such as Japan (7), and many central and South American countries, such as Nicaragua and Brazil in particular (8).

In addition to protein, legumes are excellent sources of fiber, resistant starch, and certain vitamins and minerals such as folate and potassium, the latter of which is a nutrient of concern (9). U.S. potassium intake is only about one-half the dietary recommended intake (10). In addition, many legumes also have a very high antioxidant content, with oxygen radical absorbance capacity values equaling those of fruits touted for their antioxidant activity (11). Also, despite their high-carbohydrate content, the glycemic load of beans is relatively low because of their low glycemic index (12).

There is arguably some question about the extent to which some soy protein products mimic legumes in a way that warrants their classification in the vegetable group (e.g. they are low in soluble fiber). But clearly both the traditional soyfoods and the soy protein products are excellent sources of protein. In fact, compared with other legumes, soybeans are much higher in protein (13) and the quality of soy protein is superior (protein digestibility correct amino acid scores typically range between

0.9 and 1.0) (14). Not unexpectedly, given the high protein digestibility corrected amino acid scores, the digestibility of soy protein is quite high, typically $\geq 90\%$, and the indispensable amino acid concentration (mg/g protein) of soy protein exceeds the dietary requirements (15). Soybeans are also much higher in fat ($\sim 40\%$ of total energy) (13) than most legumes, which are almost fat free. The predominate fatty acid in soy is the essential (n-6) fatty acid, linoleic acid ($\sim 56\%$), but the soybean is also one of the few plant sources of the essential (n-3) fatty acid, α -linolenic acid (~ 7 or 8% of total) (16).

Thus, soyfoods can be viewed as a healthful means by which to meet protein requirements. Especially so because higher protein diets may adversely affect renal function in susceptible individuals (17,18), the number of which is increasing along with the diabetes epidemic (19). Compared with animal protein, there is evidence suggesting soy protein has less of an adverse effect on renal function as measured by changes in glomerular filtration rates and albumin excretion (20,21).

Because soyfoods may be substituted for more traditional sources of protein in Western diets, which are typically good sources of minerals such as iron and zinc, it is important to understand the impact of soyfoods on mineral balance. Zinc absorption from soyfoods is only modestly lower than that from animal sources, although soybeans are not a particularly good source of this nutrient (22,23). In contrast, soyfoods are quite high in iron (24). Until recently, it was thought that the iron in all plant foods, including soyfoods, was poorly absorbed. However, research utilizing improved methodology indicates that iron absorption from soy may be quite high, because most of the iron in soy is in the form of ferritin (25,26). Finally, despite containing both phytate and oxalate, components that inhibit calcium absorption, calcium absorption from soybeans (27) and, most importantly, from calcium-fortified soymilk is similar to calcium absorption from cow milk (28).

Soy and chronic disease risk

Introduction. Despite the generally desirable nutritional attributes of soyfoods, nutrient content has little to do with the intense research interest in soy that first began 20 y ago. Much of this interest is because the soybean is essentially a unique dietary source of isoflavones (29). In total, there are 12 different soybean isoflavone isomers. These are the 3 aglycones, genistein (4',5,7-trihydroxyisoflavone), daidzein (4',7-dihydroxyisoflavone), and glycitein (7,4'-dihydroxy-6-methoxyisoflavone); their respective β -glycosides, genistin, daidzin, and glycitin; and 3 β -glucosides, each esterified with either malonic or acetic acid (30,31). Most current discussion about isoflavones focuses on their ability to bind to estrogen receptors, which has been recognized for >40 y (32). However, initial recent interest in isoflavones was sparked by the ability of genistein to inhibit in vitro the activity of tyrosine protein kinase, an enzyme often overexpressed in cancer cells (33). There continues to be much interest in the ability of genistein to affect genes related to the control of cell growth independent of binding to estrogen receptors (34).

Breast cancer. Much of the isoflavone research has focused on cancer prevention; in 1991, isoflavones were identified as 1 of 5 putative chemopreventives in soy (35). Not surprisingly, because of the historically low breast and prostate cancer mortality rates in Asia, these 2 cancers have received the bulk of the attention (36). A recent meta-analysis by Wu et al. (37) found that high soy intake was associated with an odds ratio (OR) of 0.71 (95% CI = 0.60–0.85) for breast cancer when comparing high and low

³ Abbreviations used: BMD, bone mineral density; CHD, coronary heart disease; ISP, isolated soy protein; LDLC, LDL cholesterol; OR, odds ratio.

soy intake. However, as recently reviewed by Messina and Wu (38) and Messina and Hilakivi-Clarke (39), there is an intriguing body of evidence suggesting that to derive protection against breast cancer, soy consumption must occur during childhood and/or adolescence. All 4 epidemiologic studies examining this hypothesis reported protective effects with reductions in risk ranging from 28 to 60% (40–43).

The hypothesis that early soy intake reduces breast cancer risk was first proposed by Lamartiniere et al. (44) in 1995 on the basis of findings in rodents. The current operating hypothesis is that isoflavone exposure stimulates differentiation of breast tissue, which leads to a reduction in the anatomical structures that give rise to cancer cells. Therefore, although the epidemiologic studies assess the impact of traditional soyfoods, there is little reason to conclude more processed products containing similar amounts of isoflavones would not be equally protective.

Generating clinical support for the early soy intake hypothesis is clearly a high-priority research need. Nevertheless, even without these data, because the potential public health benefit is so great and the dietary behavior required for deriving the proposed benefit so minimal and easily achieved, there appears little reason for health professionals not to encourage girls and female adolescents to consume 1 serving/d of soy, the approximate amount associated with protective effects in epidemiologic studies.

Prostate cancer. Similar to the results of Wu et al. (37) for breast cancer, a meta-analysis by Yan and Spitznagel (45) reported a combined relative risk/OR of 0.74 ($P = 0.01$) for prostate cancer when comparing high with low soy intake. Even more impressive, when analyzed separately, the combined relative risk and OR for studies involving Asian and Western populations were 0.52 ($P = 0.01$) and 0.99 ($P = 0.91$), respectively. Despite the ability to identify significant associations between soy/isoflavone intake and health outcomes in epidemiologic studies involving typical Western populations, it is likely that because of the negligible soy intake, these associations do not have a causal basis (46). In agreement with the meta-analysis, animal studies generally show isoflavone-containing diets retard the development of prostate cancer (47).

There is also suggestive evidence that isoflavones inhibit prostate tumor spread. For example, genistein markedly inhibited prostate tumor metastasis in mice (48) and a recent pilot study found that in prostate cancer patients, genistein exposure decreased levels of matrix metalloproteinase-2 transcripts in normal prostate cells from prostate cancer-containing tissue, suggesting genistein can inhibit cell invasion (49). This latter finding clearly warrants follow-up research. Because prostate tumors are slow growing and are typically diagnosed late in life, even modestly delaying tumor onset and/or growth can profoundly affect prostate cancer mortality. As was the case for breast cancer, the operating hypothesis is that if soyfoods reduce prostate cancer risk, it is because they contain isoflavones.

Coronary heart disease. In 1999, the U.S. FDA awarded a health claim for soy protein and coronary heart disease (CHD) based on its cholesterol-lowering effects (50). The threshold intake for cholesterol reduction was established at 25 g/d, although there is evidence lower amounts may also be efficacious (51). However, questions have recently been raised about the efficacy of soy protein (52) and, in fact, the FDA is currently reevaluating evidence in support of the health claim, although this reevaluation was undertaken because of the large number of clinical studies published within the past

decade, not because these studies are not supportive of the claim.

Meta-analyses and reviews published between 2004 and 2007 have concluded that soy protein lowers LDL cholesterol (LDLC) by 3–5% (52–54), which is similar to the effects of soluble fiber (55). From a public health perspective, even this modest reduction is meaningful, because in theory, over time, each 1% decrease in LDLC reduces CHD risk and/or mortality by as much as 2–5% (56,57). Not surprisingly, comprehensive dietary approaches that have resulted in reductions in LDLC ranging from 20 to 30% have relied heavily on soyfoods; the high quality of soy protein and its hypocholesterolemic effects combined with the favorable fatty acid profile of soyfoods make these foods especially attractive in such diets (58).

Independent of effects on blood cholesterol, there is intriguing evidence from Asian epidemiologic studies suggesting soyfoods exert coronary benefits (59–61). In support of these data are clinical studies showing soyfoods, soy protein, or soybean isoflavones favorably affect a number of biological measures that influence heart disease risk (62,63). However, with one exception, the inconsistent and/or limited clinical data prevent conclusions from being made about the effects of soy on these measures. A recently published meta-analysis found that isoflavones consistently improve endothelial function as measured by changes in flow-mediated dilation in participants with impaired, but not normal, endothelial function at baseline (64).

Finally, a meta-analysis by Hooper et al. (62) found that both ISP and soyfoods lowered blood pressure, but the effect of the latter was about twice that of the former. However, additional clinical studies are needed before conclusions can be made. Further, direct comparisons, not comparisons across studies, are needed to understand any possible loss in hypotensive properties as a result of processing.

Osteoporosis. The well-recognized skeletal benefits of estrogen therapy for postmenopausal women provide a theoretical basis for exploration of the possible skeletal benefits of isoflavones (65). More than 25 studies have examined the effects of isoflavone-containing products on bone mineral density (BMD) in postmenopausal women, although most trials were no longer than 1 y in duration and involved fewer than 50 women/group. An important exception is a 2-y trial conducted by Italian investigators that found that in postmenopausal osteopenic Italian women given 54 mg/d genistein (the amount provided by ~4 servings of soyfoods), spinal BMD increased by 5.8% ($n = 150$), whereas it decreased in the placebo group by 6.3% ($n = 154$). Similar effects were noted at the hip. Differences between groups were even greater during the 3rd y of the study, in which approximately one-half of the women participated (66).

However, in contrast to these results are those from several recently published long-term trials (67–69). Most notable are the results of a 3-y trial by Alekel et al. (70) that included, in addition to the placebo group, 2 groups of postmenopausal women who were given either 80 or 120 mg/d isoflavones; only at the highest dose did isoflavones exhibit even a modest benefit at only the femoral neck. Disappointing results were also recently published by Weaver et al. (71) in which a very sensitive assay was used to assess the antiresorptive effects of isoflavones.

In contrast to the results from recent clinical studies are the findings from both of the prospective epidemiologic studies that examined the relationship between soyfood intake and fracture risk among postmenopausal women. In the Shanghai cohort, over the 4.5-y follow-up period there were 1770 fractures

among the 24,403 women (72) and in the Singapore cohort, there were 692 hip fractures among 35,298 women over a period of 7.1 y (73). Interestingly, despite much lower isoflavone intakes in the latter study, both reported one-third reductions in risk when comparing high- with low-soy consumers.

There are several possible explanations for the contrasting results between the epidemiologic and intervention studies, including differences in exposure period (Asian adult soy intake assessed in the epidemiologic studies may reflect lifelong intake) and soy components other than isoflavones providing skeletal benefits. To clinically test the findings of the epidemiologic studies, even using changes in BMD rather than fractures as an endpoint, would require intervening with traditional soyfoods for a 2- to 3-y period.

Menopausal symptoms. In 1992 Adlercreutz et al. (74) suggested that the low prevalence of hot flashes reported by Japanese menopausal women might be at least partially due to their high consumption of soyfoods. Speculation was that the estrogen-like effects of isoflavones might mitigate the drop in estrogen levels, one trigger for hot flashes, that occurs when women enter menopause. More than 50 hot flash trials evaluating the efficacy of isoflavone-containing products have been conducted. Most analyses have found suggestive evidence supporting the efficacy of isoflavones but did not reach definitive conclusions because of the conflicting data (75,76).

It can be argued, however, that even the inconsistent data are sufficiently encouraging to justify health professionals recommending the use of isoflavones, because any benefit can be subjectively determined and will likely be apparent within just a few weeks. Further, the overall benefit (including placebo response) in most studies is an ~50% reduction in the severity and/or frequency of hot flashes. This degree of improvement is similar to that wanted by women seeking nonhormonal alternatives to estrogen for menopausal symptom relief (77).

Importantly, a recently presented systematic review and meta-analysis of the hot flash literature found that 7 of 9 of the high-genistein isoflavone supplement studies and 4 of 6 low-genistein isoflavone studies reported significant benefit (Kurzer MS, Messina M, unpublished data). High-genistein isoflavone supplements were more potent than low-genistein isoflavone supplements; the overall effect of the former was to reduce frequency and severity by ~19 and 32%, respectively, beyond the placebo effect. Because only supplements were evaluated, it is not clear the results apply to whole soyfoods, although there is no obvious reason why they would not given equal isoflavone content.

Areas in dispute. There appears to be general agreement within the scientific community that with the exception of those with soy allergies, adding whole soyfoods to the diet in amounts consistent with Asian intake is commendable (52). On the other hand, in recent years, concerns have been raised that soyfoods might be contraindicated for certain subpopulations. Two analyses of the clinical data that considered adverse effects concluded only that the incidence of minor gastrointestinal disturbances might be higher in soy consumers (53,78).

Most of the concern about soy has focused on its consumption by breast cancer patients and women at high risk of developing breast cancer because of the estrogen-like properties of isoflavones. However, the animal research that forms the basis for these concerns shows minimally (soy flour) processed soy does not stimulate tumor growth (79). Thus, not even these data argue against the use of traditional soyfoods. This position is consistent with that of the American Cancer Society (80). Furthermore, regardless of the form in which exposure occurs, isoflavones do

not adversely affect markers of breast cancer risk, including breast tissue density, breast cell proliferation, and circulating estrogen levels [see for review (81)]. Perhaps even more importantly, recently published epidemiologic studies indicate that the consumption of traditional soyfoods after a diagnosis of breast cancer has no effect on or actually improves prognosis (82-84).

The estrogen-like effects of isoflavones have also raised concern that soyfoods exert feminizing effects in men, such as causing gynecomastia (85) and reducing circulating testosterone levels (86) and sperm concentration (87). However, the totality of evidence, especially the clinical data, indicate feminization concerns are unwarranted; feminizing effects or not observed in response to isoflavone exposure equal to or greatly exceeding typical Asian intake regardless of whether exposure occurs via supplements or traditional soyfoods [see reference (88) for a review of this topic].

Another area of concern has to do with the effects of isoflavones on thyroid function. Concerns are based primarily on in vitro and animal studies involving isolated isoflavones (89). In the early 1960s, several cases of goiter were attributed to the use of soy infant formula, but this problem was eliminated soon thereafter when soy formula was fortified with iodine (90-92). The totality of the evidence clearly shows that isoflavones do not adversely affect thyroid function in iodine-replete euthyroid individuals (93). Soyfoods may slightly increase the amount of thyroid medication needed by patients with hypothyroidism because of an inhibitory effect on drug absorption (94-97), but this is also true for food in general, many herbs and drugs, and fiber supplements (98). It is not necessary for thyroid patients (with the exception of infants with congenital hypothyroidism) to avoid soyfoods, because medication is taken on an empty stomach and dosages can easily be adjusted to compensate for any effects of soy.

There are, however, 2 clinical situations in which the relationship between soy intake and thyroid intake has not been explored that warrant investigation. One involves individuals with subclinical hypothyroidism, which represents ~5-10% of U.S. postmenopausal population, and the other involves individuals with iodine deficiency (99). Iodine intake is typically quite good in the United States, although certain subpopulations may be at risk of deficiency (100). When individuals whose iodine intake is inadequate are identified, the appropriate recommendation is to increase iodine intake, not to avoid soyfoods. Subclinical hypothyroidism is defined as having normal levels of the 2 primary thyroid hormones, thyroxine and triiodothyronine, but elevated levels of thyroid stimulating hormone (101). There is a need to evaluate the effect of soyfoods on individuals with this condition.

Finally, 2 epidemiologic studies have raised concern about possible detrimental effects of soy on cognitive function. One was a prospective study (begun in 1965 as the Honolulu Heart Study) published in 2000 that found tofu consumption was associated with impaired cognitive function in Japanese men and their spouses residing in Hawaii (102). The other is an Indonesian cross-sectional study that found that worse memory, as measured using a word learning test sensitive to dementia, was associated with high tofu consumption (103). Interestingly, tempeh consumption was independently related to better memory, particularly in participants over 68 y of age. In contrast to these 2 studies are the results of a cross-sectional study conducted in Hong Kong, which found that among women aged ≥ 65 y, isoflavone intake was unrelated to cognitive function (104).

The Hawaiian and Indonesian studies had several noteworthy limitations. For example, in the former study, the intake of only

26 foods was assessed and questions about tofu intake were not consistent over the course of the follow-up period (102). In the Indonesian study, 2 isoflavone-rich soyfoods had opposite effects (103). The authors of this study suggested the high-folate content of tempeh, but not tofu, was responsible for the differing findings, but this explanation appears unlikely. A more likely explanation, also discussed by the authors, is the presence of formaldehyde in tofu, a known toxin shown to adversely affect memory in rodents (105) and urinary levels of which are markedly elevated in dementia patients (106). In Indonesia, tofu production is a cottage industry and despite attempts to prevent its use, formaldehyde is sometimes used as a preservative.

Since 2001, at least 8 different clinical studies evaluating the cognitive effects of soyfoods or isoflavones have been conducted, most of which have involved postmenopausal women. As reviewed by Zhou et al. (107), these data provide some reason for optimism about the potential cognitive benefits of isoflavones. However, at this point, no conclusions about the relationship between soy and cognition can be made and the existing preliminary data in this area are an insufficient basis upon which to make recommendations about soy intake.

Summary and Conclusions

Soyfoods represent first and foremost a healthful means by which to obtain protein and to add diversity to the diet, because most Americans consume legumes to a very limited extent. Independent of nutrient content, evidence in support of soyfoods providing health benefits such as reducing the risk of various chronic diseases ranges from very speculative to very encouraging. Overall, with the exception of those who are allergic, there is little evidence soyfoods are contraindicated for any individual. In the same way that nutritionists recommend whole grains over refined grains and apples over apple juice, minimally processed soyfoods should be emphasized over more highly-processed forms of soy. However, the latter can still be healthful options for those interested in incorporating more soy into their diet.

No food should play too large a role in the diet and soyfoods, while extremely convenient, are just one of many legumes available to the public. The soy intake associated with a range of benefits in Asian epidemiologic studies, from reductions in CHD risk (59–61) to protection against prostate cancer (45), is ~2 servings/d. Clinical studies that have shown benefits of isoflavones, such as improvements in endothelial function, have generally used isoflavone doses of between 50 and 100 mg/d, amounts provided by between 2 and 4 servings of traditional soyfoods (64). Thus, a reasonable goal for consumers who may be unfamiliar with soy and are interested in moving toward a more plant-based diet, improving overall diet quality, and deriving the proposed health benefits of soyfoods is to consume 2 servings of traditional soyfoods per day (~15–20 g protein, 50–75 mg isoflavones), although optimal amounts may be somewhat higher. At these levels, soy protein would represent ~20–25% of total dietary protein intake; therefore, this recommended intake is consistent with the dietetic principles of diversity and moderation.

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