Health Effects of Soy Protein and Isoflavones in Humans\textsuperscript{1–3}

Chao Wu Xiao\* 

Nutrition Research Division, Food Directorate, Health Products and Food Branch, Health Canada, 2203E Banting Research Centre, Ottawa, Canada K1A 0L2; and Department of Cellular and Molecular Medicine, Faculty of Medicine, University of Ottawa, Ottawa, Canada

Abstract

Epidemiological investigations suggest that soy consumption may be associated with a lower incidence of certain chronic diseases. Clinical studies also show that ingestion of soy proteins reduces the risk factors for cardiovascular disease. This led to the approval of the food-labeling health claim for soy proteins in the prevention of coronary heart disease by the U.S. FDA in 1999. Similar health petitions for soy proteins have also been approved thereafter in the United Kingdom, Brazil, South Africa, the Philippines, Indonesia, Korea, and Malaysia. However, the purported health benefits are quite variable in different studies. The Nutrition Committee of the American Heart Association has assessed 22 randomized trials conducted since 1999 and found that isolated soy protein with isoflavones (ISF) slightly decreased LDL cholesterol but had no effect on HDL cholesterol, triglycerides, lipoprotein(a), or blood pressure. The other effects of soy consumption were not evident. Although the contributing factors to these discrepancies are not fully understood, the source of soybeans and processing procedures of the protein or ISF are believed to be important because of their effects on the content and intactness of certain bioactive protein subunits. Some studies have documented potential safety concerns on increased consumption of soy products. Impacts of soy products on thyroid and reproductive functions as well as on certain types of carcinogenesis require further study in this context. Overall, existing data are inconsistent or inadequate in supporting most of the suggested health benefits of consuming soy protein or ISF. J. Nutr. 138: 1244S–1249S, 2008.

Introduction

Soy foods have been consumed for centuries in Asian countries. Many potential benefits have been linked to intake of soy products according to epidemiological investigations (1). For instance, consumption of soy foods may contribute to lower incidences of coronary heart diseases, atherosclerosis, type 2 diabetes, and decreased risk of certain types of carcinogenesis such as breast and prostate cancers as well as better bone health and relief of menopausal symptoms. Animal (2,3) and human (1,4) studies have also shown that consumption of soy protein or associated isoflavones (ISF)\textsuperscript{4} has beneficial impacts on the risk factors for cardiovascular disease including lowering liver or blood triglyceride, total and LDL cholesterol levels, increasing HDL cholesterol and the ratio of HDL/LDL cholesterol. Cellular and molecular biology studies have demonstrated that soy components modulate the key transcription factors involved in the regulation of lipid metabolism and their regulated downstream gene expression in animals and in vitro cultured human cells at transcriptional or posttranslational levels (3,5–7).

Production and consumption of soy foods within Western countries have increased dramatically in the last decade, especially after the approval of a food-labeling health claim for soy proteins in the prevention of coronary heart disease by the U.S. FDA in 1999 (8). To date, similar petitions have also been approved in 8 other countries including Japan in 1996, the United Kingdom in 2002, South Africa in 2002, the Philippines in 2004, Brazil in 2005, Indonesia in 2005, Korea in 2005, and Malaysia in 2006 (Table 1). However, the most recent human results obtained since 1999 show some inconsistencies in the

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\textsuperscript{*} To whom correspondence should be addressed. E-mail: chaowu_xiao@hc-sc.gc.ca.

\textsuperscript{4} Abbreviations used: ER, estrogen receptor; ERE, estrogen response element; ISF, isoflavone; PSA, prostate-specific antigen.
lipid-lowering functions of soy, especially the magnitude of the effects. Moreover, studies on the other potential health benefits of soy such as prevention of postmenopausal bone loss, certain types of cancers, and diabetes and relief of menopausal symptoms remain inconclusive (9). Meanwhile, the potential adverse effects of certain soy components observed in animal and human studies such as antithyroid actions, endocrine disruption, and carcinogenesis enhancement potential are not well understood but are increasingly becoming a concern for soy consumers, health professionals, and policy makers. The purpose of this article is to overview current knowledge concerning health benefits and potential adverse effects of consuming products containing soy proteins and associated ISF.

**Soy protein and ISF**

Soybeans contain 35–40% protein on a dry-weight basis, of which 90% is comprised of 2 storage globulins, 11S glycinin and 7S β-conglycinin (10). Glycinin has A (acidic) and B (basic) subunits, whereas β-conglycinin has α, α’, and β subunits. These proteins contain all amino acids essential to human nutrition, which makes soy products almost equivalent to animal sources in protein quality but with less saturated fat and no cholesterol (11).

ISF are the other most studied compounds that are biologically active in soybeans and are closely associated with the proteins. ISF are major soy phytoestrogens present in soy foods and require washing in alcohol for removal (12). Soy foods and soy-based infant formulas are rich sources of ISF and contain ~1–4.2 mg ISF/g, whereas soy ISF supplements contain up to 500 mg ISF/g. Genistin, daidzin, and glycitein are the main soy ISF. Both genistin and daidzin are conjugated to sugars as glycosides in soybeans and most soy foods consumed in the Western countries. Glycoside ISF cannot be absorbed unless hydrolyzed and converted to the bioactive forms, genistein and daidzein, both aglycones, by intestinal microflora or in vitro fermentation (13). Most traditional Asian soy foods contain high levels of aglycone ISF that are more bioavailable and active than the glycoside ISF.

ISF are structurally similar to mammalian estradiol (14,15) and can bind to both α and β isomers of estrogen receptor (ER). However, their binding affinity to ERβ is ~20 times higher than that to ERα, and their efficacies of activating the binding of ERβ to estrogen response elements (ERE) of target genes are 500–850 times higher than that of activating the binding of ERα to ERE (16). ERα and ERβ share little or no homology between their ligand-binding and N-terminal transactivation domains. This feature may contribute to their opposite effects on regulating gene expression and physiological functions. For example, estrogenic compounds stimulate proliferation of human breast cancer cells through binding to ERα but suppress proliferation via ERβ (17). Therefore, the selective receptor binding may confer on ISF the ability to regulate physiological functions in a different way from estrogen.

**Soy consumption across different populations**

The mean daily intakes of soy protein are ~30 g in Japan, 20 g in Korea, 7 g in Hong Kong, 8 g in China, and <1 g in the United States (18,19). The mean ISF consumption is 11–47 mg/d in Asian countries (19–21), 1–2 mg/d in Western countries (22,23), and 22–45 mg/d in 4-mo-old infants fed soy formulas (24).

Mean plasma concentrations of ISF are 1640 nmol/L for genistein and 1160 nmol/L for daidzin in infants fed soy formulas (25), 492.7 nmol/L for genistein, 282.5 nmol/L for daidzin, and 99.1 nmol/L for equol in Japanese men, and 33.2 nmol/L for genistein, 17.9 nmol/L for daidzin, and 0.57 nmol/L for equol in British men (26). These data indicate that soy-formula-fed infants are a group exposed to the highest amount of soy ISF.

**Hypolipidemic effects of soy protein and ISF**

The first human study on the cholesterol-lowering effect of soy protein was reported in 1967 (27) and demonstrated that replacement of mixed proteins by mainly isolated soy protein products at an intake of 100 g/d reduced mean cholesterol levels by >2.59 mmol/L in hypercholesterolemic men. However, health professionals did not pay particular attention to this benefit until a meta-analysis was published in 1995. Anderson et al. (1) analyzed 38 controlled clinical studies published between 1977 and 1994. Among them, 30 studies were conducted with hypercholesterolemic subjects. The results suggested that mean intakes of 47 g/d, ranging from 17 to 124 g, of isolated or textured soy protein resulted in significant reduction

### TABLE 1 Health claims for soy protein in different countries

<table>
<thead>
<tr>
<th>Country</th>
<th>Description</th>
<th>Status</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malaysia</td>
<td>Soy protein helps reduce cholesterol levels.</td>
<td>Approved in 2006</td>
<td>(65)</td>
</tr>
<tr>
<td>Japan</td>
<td>Helps improve diet for those with high cholesterol level.</td>
<td>Approved in 1996</td>
<td>(66)</td>
</tr>
<tr>
<td>Korea</td>
<td>Soy protein helps improve elevated levels of blood cholesterol.</td>
<td>Approved in 2005</td>
<td>(66)</td>
</tr>
<tr>
<td>France</td>
<td>Soy protein, as part of a diet low in fat and saturated fat, may reduce blood cholesterol.</td>
<td>Under review</td>
<td>(66)</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>The inclusion of at least 25 g of soy protein per day, as part of a diet low in saturated fat, can help reduce blood cholesterol levels.</td>
<td>Approved in 2002</td>
<td>(67)</td>
</tr>
<tr>
<td>Brazil</td>
<td>Daily consumption of at least 25 g of soy protein could help the cholesterol reduction. Its consumption should be associated with a balanced diet and a healthy lifestyle.</td>
<td>Approved in 2005</td>
<td>(66)</td>
</tr>
<tr>
<td>Canada</td>
<td>The consumption of 25 g of soy protein per day reduces the risk of heart disease. This product contains ___ grams of soy protein per serving.</td>
<td>Under review</td>
<td>(66)</td>
</tr>
<tr>
<td>South Africa</td>
<td>Diets which contain at least 25 g soy protein (4 servings) daily and which are low in saturated fat and cholesterol may reduce the risk of heart disease by lowering cholesterol levels.</td>
<td>Under revision</td>
<td>(66)</td>
</tr>
<tr>
<td>United States, Philippines, Indonesia</td>
<td>25 g of soy protein a day, as part of a diet low in saturated fat and cholesterol, may reduce the risk of heart disease. A serving of [name of food] supplies ___ g of soy protein.</td>
<td>Approved in 1999, 2004, 2005</td>
<td>(8,66)</td>
</tr>
</tbody>
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in total cholesterol by 9.3%, LDL-cholesterol by 12.9%, and triglycerides by 10.5%, with an insignificant change in HDL-cholesterol levels, compared with animal protein.

The U.S. FDA approved a food-labeling health claim for soy protein in the prevention of coronary heart disease in 1999 but clearly indicated that “the evidence did not support a significant role for soy ISF in cholesterol-lowering effects of soy protein” (8). Since then, retail soy consumption has significantly increased. Sales of U.S. soy foods doubled in 6 y, from $2 billion in 1999 to $4.3 billion in 2005. Within the last 10 y, the number of soy products has also increased from hundreds to 3000. From 2000–2007, food manufacturers in the United States have introduced over 2700 new foods with soy as an ingredient, including 479 new products introduced in 2006 alone (28). This has led to extensive research on the beneficial and potential adverse effects of soy intake.

The Nutrition Committee of the American Heart Association has assessed 22 randomized trials published since 1999 (9). Among them, 19 studies were conducted with hyperlipidemic subjects. Results show that mean consumption of 50 g/d, ranging from ~25 to 133 g, of isolated soy protein containing ISF lowered LDL cholesterol levels by 3% in comparison with milk or other proteins. However, no significant effects on circulatory levels of HDL cholesterol, triglycerides, lipoprotein(a), or blood pressure have been found. Among a subgroup of 19 studies, the mean effects of soy ISF on LDL cholesterol and other lipid risk factors were insignificant (9). A recent study in postmenopausal women showed that daily supplementation of 25 g of soy protein and 101 mg of aglycone ISF lowered LDL cholesterol and apolipoprotein B levels by 11% and 8%, respectively, and reduced systolic and diastolic blood pressure by 9.9% and 6.8%, respectively, in hypertensive women (29).

**Soy consumption and bone health**

Meta-analyses of randomized controlled trials suggest that soy ISF intervention significantly attenuates bone loss of the spine (30) and markedly decreases urinary deoxypyridinoline, a bone resorption marker, and increases serum bone-specific alkaline phosphatase, a bone formation marker, in menopausal women (31). Studies in postmenopausal women have shown similar results (32–34). However, no significant effects of ISF on bone mass density or biomarkers of bone metabolism have been reported in other studies in which soy protein was supplemented and ISF-poor soy protein was used as control (35–37). These data indicate that soy protein may interfere with the effects of ISF either by masking or antagonizing its effect. A nonsoy control group would address this issue in future studies. Although increasing data, especially those from more recent studies, tend to support a positive role of soy intake in the prevention of bone loss, especially on the biomarkers of bone metabolism, in postmenopausal women, more human trials are needed to verify this action. Currently, there is no existing health claim for bone health of soy intake.

**Effects of soy consumption on menopausal symptoms**

A meta-analysis of 25 trials published between 1966 and 2004 indicates that soy phytoestrogens did not improve hot flashes or other menopausal symptoms (38). Intake of soy supplements for treatment of menopausal symptoms in patients with early breast cancer did not show any significant effect on menopausal symptom scores or quality of life after 12 wk compared with placebo (39). Therefore, there is no consistent evidence to support any beneficial effect of soy intake on menopausal symptoms at this stage.

**Effects of soy consumption on breast and prostate cancers**

Many animal and human studies have been conducted to determine the association between soy intake and breast and prostate cancers. A variety of human cancer cell lines have also been used in vitro studies to understand the cellular and molecular events involved in the regulation of cell proliferation and apoptosis by soy components. However, the existing results from clinical trials are inconclusive.

Case-control studies have shown that high soy intakes in adolescence are associated with low risk for breast cancer in adulthood (40). But a recently published Japanese collaborative cohort study suggested that consumption of soy foods such as tofu, boiled beans, and miso soup has no protective effects against breast cancer (41). Moreover, soy ISF may stimulate epithelial cell proliferation in the breasts of premenopausal women in clinical studies (42).

Dietary ISF significantly decreased the risk of prostate cancer in Japanese men (43). Supplementation with soy protein or soy ISF decreased the markers of cancer development and progression in prostate cells including prostate-specific antigen (PSA), testosterone, and androgen receptor in patients with prostate cancer (44,45) or in men at high risk for developing advanced prostate cancer (46). However, soy intake at the levels of 44 g of soy protein and 116 mg ISF daily failed to change the serum total or free PSA in healthy middle-aged men (47). These results suggest that consumption of soy protein or soy ISF may affect PSA only in prostate cancer patients or high-risk men but not in normal subjects. Further investigations are essential for a better understanding of the association of soy-induced reduction in PSA expression and decreased risk of prostate cancer.

**Effects of soy on endocrine functions**

**Antithyroid effect.** Excessive soy intake has been reported to be responsible for the development of goiter, including thyroid enlargement, in both iodine-deficient rodents (48–51) and infants fed soy-flour-based formula without iodine fortification (52–54). Animals fed a soy diet require almost twice as much iodine compared with animals not fed soy (49,55,56). Infants with congenital hypothyroidism who consume soy formula require ~25% more synthetic hormone than those on soy-free formulas (57,58). Additionally, soy components dramatically stimulate the development of thyroid hyperplasia in iodine-deficient rats (59,60). Our studies in rats have shown that consumption of 20% alcohol-washed soy protein isolate containing minimal amounts of ISF markedly suppressed the binding ability of hepatic thyroid hormone receptor to the thyroid hormone response element of the target genes (6,61). These findings suggest that intake of soy may reduce the efficiency of thyroid hormone function and that soybeans may contain goitrogens that can interfere with the utilization of iodine or functioning of the thyroid gland and cause thyroid problems. However, it appears that consumption of soy could cause goiter only in animals or humans consuming diets marginally adequate in iodine or who were predisposed to develop goiter (62), and in most cases dietary supplementation with adequate iodine can reverse the disorders (63).

**Reproductive functions.** In the United States and Canada, over 20–25% of formula-fed newborns are fed soy-based formulas for various reasons such as bovine milk allergies. These infants represent a group exposed to a large amount of soy ISF. Blood ISF concentrations in those infants are 13,000–22,000 times higher than plasma estradiol levels in early life and are 6- to 11-
fold higher on a body-weight basis than the dose that has hormonal effects in adults consuming soy foods (25). However, the impact of excessive intake of ISF on early development and on endocrine and reproductive functions in humans remains unclear.

Summary of scientific evidence and current status for developing health claims

Consumption of soy protein appears to consistently lower blood LDL cholesterol in hyperlipidemic subjects. However, the magnitude of the effect and the required intake to achieve the effect are variable in different studies. Increasing evidence, especially in light of results from recent human studies, tends to support the beneficial effects of soy ISF in the prevention of bone loss in postmenopausal women. Although soy protein or ISF positively impact biomarkers of prostate cancer, their potential benefits have not been substantiated in clinical trials. The effects of soy protein and ISF in relieving menopause symptoms and prevention of breast cancer are not evident. The antithyroid actions of soy appear to be consistent in both animals and humans. Present evidence indicates that soy protein may be responsible for at least the hypolipidemic effects of soy consumption. However, whether the effect is caused by amino acid composition or protein subunits or composite peptides remains unclear. It has been shown that different processing procedures in the preparation of soy protein isolates affect the intactness of protein subunits, which might be crucial for the biological functions of soy proteins (64). Therefore, adequate characterization of the soy protein used in future studies, such as assessing the intactness and measuring the relative abundance of each protein subunit, will be extremely useful in making the results from different studies comparable. Health claims for a possible association between consuming soy protein and reduced blood cholesterol levels or decreased risk for heart disease have been approved in 9 countries since 1996. A similar petition was rejected by the Netherlands and remains under review in France and Canada. Although a broad spectrum of health benefits have been suggested to be attributable to soy consumption, consistent and direct evidence to support these effects are lacking or inadequate in most of the cases. Future studies should pay more attention to identification of the bioactive components in soy and elucidation of the molecular mechanisms involved.

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Other articles in this supplement include references (68–77).

Literature Cited


