# Soy and Women's Health



2010 EDITION

Traditional soyfoods such as tofu and miso have been widely used in many East Asian countries for centuries and have been consumed by health-conscious individuals in Western countries for several decades. In recent years, because of their purported health benefits, increased numbers of Westerners have decided to incorporate soy into their diets. Soyfoods hold particular appeal for postmenopausal women because they are essentially unique dietary sources of isoflavones, one type of phytoestrogen.

Isoflavones exhibit estrogen-like effects under certain experimental conditions and have been posited to reduce the risk of coronary heart disease[1] and osteoporosis[2] and to alleviate menopause-related hot flashes.[3] Consequently, many women view soyfoods as natural alternatives to conventional hormone therapy. Women who use alternative therapies express a desire to have control over their symptoms and the way in which their menopause is treated.[4] Not surprisingly, interest in alternatives has risen following the publication of the results from the Women's Health Initiative trial in 2002, which showed that the risk of long-term use of combined hormone therapy (estrogen plus progestin) outweighed the benefits.[5]

However, isoflavones are not without controversy. Their estrogen-like effects have raised concern that these soybean constituents possess some of the same undesirable properties as hormone therapy. In particular, there is controversy about whether soyfoods are contraindicated for breast cancer patients and women at high risk of developing this disease.[6] In the text that follows, the health effects of soyfoods for postmenopausal women are discussed.

## Overview of Isoflavones

Isoflavones have a very limited distribution in nature such that diets that do not include soyfoods are almost devoid of these compounds.[7] Not surprisingly, whereas average isoflavone intake among adults ranges from about 30-50 mg per day in Japan and Shanghai, China,[8] it is less than 3 mg per day in the United States and other Western countries.[9-15] Each gram of soy protein in soybeans and unprocessed soyfoods is associated with approximately 3.5 mg of isoflavones.[8] Consequently, one serving of a traditional soyfood, such as three to four ounces of tofu or one cup of soymilk, typically provides about 25 mg of isoflavones.

Soy protein is present in a wide range of commonly consumed foods in the United States. However, isoflavone exposure from these foods is almost negligible for two reasons. First, the amount of soy protein in these foods is quite small because it is added for functional not nutritional purposes such as bleaching, moisture retention, inhibiting oxidation and improving texture. And second, the isoflavone concentration of the soy protein used in this way is generally quite low in comparison to traditional soyfoods.

The two primary soybean isoflavones are genistein and daidzein.[16] In soybeans, a third isoflavone, glycitein, is present in relatively small amounts. The three isoflavones genistein, daidzein and glycitein comprise approximately 50, 40 and 10 percent respectively of the total isoflavone content of soybeans. Isoflavones are naturally present as the glycosides genistin, daidzin and glycitin, in which a sugar molecule is attached to the basic isoflavone structure.[16] In fermented soyfoods such as miso, more of the isoflavones are present as aglycones due to bacterial hydrolysis.[16] In this document, isoflavone amounts are expressed in aglycone weights, because this is the biologically active form.

*Soyfoods are a unique dietary source of isoflavones, a phytoestrogen that may offer women heart health benefits and may help alleviate hot flashes during menopause.*

Isoflavones are diphenolic compounds with a chemical structure similar to the hormone estrogen that bind to both estrogen receptors (ER), ERα and ERß.[17, 18] Their relative binding affinity is lower than that of 17-estradiol but circulating levels of isoflavones in people consuming soyfoods are approximately three orders of magnitude higher than levels of estrogen.[19] In comparison to ERα, isoflavones preferentially bind to and transactivate ERß,[20-23] which is one reason they are generally classified as selective estrogen receptor modulators (SERMs).[24-26] SERMs have tissue selective effects. In tissues that possess estrogen receptors, they exert estrogen-like effects in some cases but either no effects or antiestrogenic effects in others. The pharmaceutical industry has for many years been actively developing SERMs; examples include tamoxifen, used in breast cancer treatment, and raloxifene, which is used for treatment of osteoporosis.[27]

From the above discussion, it is clear that isoflavones should not be equated with the hormone estrogen. The clinical literature is replete with examples of differences between these two molecules.[26, 28-47] Furthermore, isoflavones may exert potentially-relevant hormone-independent physiological effects, therefore even their classification as SERMs may be an incomplete characterization.[48] Finally, not only should isoflavones not be equated with estrogen but soyfoods should not be equated with isoflavones as the soybean, like all foods, is a collection of hundreds of biologically active molecules.[49]

## Soy, Isoflavones and Hot Flashes

Hot flashes are the most common reason given by women for seeking treatment for menopausal symptoms. For the majority of women who experience them, hot flashes begin prior to menopause and are severe and frequent in about 10-15 percent of these women.[50] Although hot flashes usually subside after six months to two years,[50, 51] many women report having them for up to 20 years after menopause.[52]

The etiology of hot flashes is not fully understood but the drop in circulating estrogen levels that occurs during menopause is certainly recognized as one factor. The low incidence of hot flashes in Japan gave rise to initial speculation that isoflavones could be useful in their prevention.[53] Even Chinese-American and Japanese-American women are about one-third less likely to report experiencing hot flashes than Caucasian women.[54] Interestingly, Asian women do report having menopausal symptoms but chilliness and shoulder aches are much more common than hot flashes, although recent evidence suggests that this may be in part because Japanese women are reluctant to report having hot flashes.[55]

*In most clinical trials, hot flash relief was achieved by ingesting 50 to 100 mg of isoflavones daily.*

Since 1995, more than 50 clinical trials have examined the impact of isoflavone-rich soyfoods or isoflavone supplements on the alleviation of menopause-related hot flashes. In recent years, investigators have gravitated toward the use of supplements rather than soyfoods to enhance compliance and reduce the complexity of study design.

The largest and longest hot flash trial, which was conducted in Italy, found that there was a 50 percent net reduction (i.e., in comparison to the placebo) in frequency in response to the administration of 54 mg per day genistein.[56] In the second year of this study, there was no further decrease in the frequency of hot flashes in the genistein group, but the severity of hot flashes continued to lessen relative to the placebo group.[57] Another large study published in 2007 found that, over the course of 10 months, isoflavones reduced the frequency of hot flashes among Brazilian women by twice that of the placebo group (62 percent versus 31 percent), a difference that was highly statistically significant.[58]

However, not all trials have reported benefits. Although some recent reviews and analyses of the literature have concluded isoflavone-rich products alleviate hot flashes,[3, 59] most have concluded that the data do not allow definitive conclusions to be made.[60, 61] Some inconsistency in the literature is expected given the small sample size of many trials and the variable placebo response.

*Research on menopause indicates that the more hot flashes a woman experiences each day, the more soy may offer relief.*

Interindividual differences in isoflavone metabolism may also be a factor.[62] In response to the ingestion of the same amount of isoflavones, serum levels of isoflavones and their metabolites differ greatly (hundreds of fold) among individuals.[63, 64]

It is reasonable to speculate that this difference in metabolism can affect the response to soyfoods, at least for health outcomes thought to be affected by isoflavones. Some of the inconsistency may also be because the two soy-derived isoflavone supplements that are available commercially and that have been used in the clinical trials have markedly different isoflavone profiles.[65] One has an isoflavone profile similar to that found in soyfoods – high in genistein and daidzein but low in glycitein whereas the other is very low in genistein and high in daidzein and glycitein. Generally speaking, genistein is considered to be much more potent than daidzein or glycitein and there is evidence that genistein is more potent than the other isoflavones for alleviating hot flashes.[66]

The most recently conducted comprehensive statistical analysis of the literature, which is thus far available only as an abstract, found that high-genistein supplements consistently alleviated hot flashes.[67] Including the placebo response, overall frequency and severity were reduced by about 50 percent. While isoflavones are less potent than estrogen, a recent survey found that among women seeking non-hormonal treatments for hot flashes this degree of benefit would be considered to be quite satisfactory.[68]

In conclusion, since substantial clinical data show isoflavones to be efficacious, there seems little reason not to recommend isoflavones for women suffering from hot flashes. If benefits are to occur, they will be apparent within four to six weeks. In most clinical trials, subjects ingested between 50 and 100 mg of isoflavones daily. These amounts are found in approximately two to four servings of traditional soyfoods.

## Osteoporosis

In response to declining estrogen levels, women can lose substantial amounts of bone mass in the decade following menopause, which markedly increases their fracture risk.[69] Estrogen therapy has been definitively shown to reduce postmenopausal bone loss and hip fracture risk by approximately one-third.[5] Initial speculation that soyfoods might promote bone health in postmenopausal women was based on the estrogen-like effects of isoflavones and early research showing that the synthetic isoflavone, ipriflavone, exerted skeletal benefits.[70]

*Continued on page 3*

The relatively low hip-fracture rates in Asian countries have also been cited as evidence for the skeletal benefits of isoflavones, but other factors may help to explain these rates.[71] For example, Asians have a shorter hip axis length, which reduces risk for fracture.[72, 73] Also, Japanese women are less likely than Western women to fall, the precipitating event for hip fracture.[74, 75] However, spinal bone mineral density (BMD) and spinal fracture rates are similar between Asians and Caucasians.[76-83] Nevertheless, the available evidence shows that, among Chinese women, high-soy consumers are less likely to report having a fracture.

Two prospective epidemiologic studies have evaluated the relationship between soy intake and fracture risk. In both, risk was reduced by approximately one-third when women in the highest soy intake quintile or quartile were compared to women in the lowest. This degree of protection is similar to that noted for estrogen therapy.[5] In one of the prospective studies, approximately 1,800 fractures of all types occurred in the 24,000 postmenopausal Shanghai women who were followed for 4.5 years.[84] In the other, there were almost 700 hip fractures (the only site studied) among the 35,000 postmenopausal Singaporean women during the seven-year follow up period.[85] Although the results of these two studies are certainly intriguing, definitive conclusions about the skeletal effects of soyfoods can only be based on the results from appropriately designed clinical studies.

Since the first clinical study to examine the effects of an isoflavone-rich product on BMD in postmenopausal women was published in 1998,[86] more than 25 trials have done so (for reviews, see references) although many involved small numbers of subjects and were conducted for relatively short durations.[87, 88] Ideally, bone trials should be at least two years in length. The results of the clinical research are quite mixed. Although one recently published meta-analyses of the data concluded that isoflavones reduce bone breakdown[89] and increase both bone formation[89] and BMD in postmenopausal women,[2] a more rigorously-conducted meta-analysis failed to provide support for the skeletal benefits of isoflavones.[90]

Among the many clinical trials, the longest and largest trial published to date (304 subjects over a period of two years) found that postmenopausal Italian women in the placebo group lost approximately six percent of their BMD at the spine and hip, whereas those women in the genistein group (54 mg per day provided as a supplement) gained approximately this much bone at both skeletal sites.[46] In fact, although intended to last only two years, among those subjects who agreed to continue for a third year, the differences between groups were even more striking.[91] These results concur with those from a two-year study that was much smaller in size.[92]

However, the results of these two studies stand in stark contrast to several recently conducted trials. For example, a one-year study involving women from three European countries failed to show that isoflavone supplements (110 mg per day) inhibit bone loss in early postmenopausal women.[93] In agreement, another one-year trial failed to show that either isoflavone supplements or isoflavone-rich soy protein affected bone loss in postmenopausal women.[94] Similarly, a recently published two-year study found soy protein, regardless of isoflavone content, failed to prevent bone loss in postmenopausal women, although this study had a large dropout rate and many women were non-compliant with the intervention.[95]

Finally, and most importantly, a large, three-year trial sponsored by the National Institutes of Health that used two different doses (80 and 120 mg per day) of isoflavone supplements found that only in response to the high dose was there a suggestion of even modest benefit.[96] These results agree with those from trials that utilized a novel methodology to examine the effects of estrogen and a variety of phytoestrogen supplements on bone resorption; only at very high doses – doses exceeding typical isoflavone exposure from soyfoods – was there any evidence of antiresorptive effects.[66]

*Fortified soymilk is a good source of isoflavones and also contains calcium, vitamin D and protein, which offer additional bone health benefits.*

Why the two epidemiologic studies show such pronounced protective effects in contrast to the clinical studies remains to be determined. But, it is worth noting that in the former studies isoflavone intake occurred via the consumption of traditional soyfoods whereas the clinical studies have generally used soy extracts – although there is no evidence this difference matters with respect to skeletal effects. It may also be that the effects noted in the epidemiologic studies result from lifelong intake as opposed to the relatively short-term intervention periods begun in adulthood in the clinical studies, although again, there is no direct evidence supporting this suggestion.

At this point, it is quite clear that no conclusions about the possible skeletal benefits of isoflavones can be made. Still, soyfoods provide high quality protein,[97] which may be important for bone health,[98] and some soyfoods are good sources of calcium as well as vitamin D.[99] Thus, soyfoods can still be part of a bone-healthy diet, but whether isoflavones offer a direct skeletal benefit remains to be determined.

## Breast Cancer

There has been considerable investigation of the role of soyfoods in reducing risk of cancer, especially cancer of the breast. To this point, a recent meta-analysis found that in Asian epidemiologic studies, higher soy intake was associated with a 29 percent decreased risk of breast cancer.[100] However, there is solid evidence indicating that to derive this benefit soy consumption must occur during childhood or adolescence.[101-103] In animal studies, when very young rodents are exposed to isoflavones, breast or mammary cells undergo a change that makes them permanently less likely to be transformed into cancer cells later in life.[101, 104, 105] This proposed mechanism may be similar to that which has been proposed for the protective effect of early pregnancy against breast cancer.[106]



*Continued on page 4*

Despite the proposed benefits, the relationship between soyfoods and breast cancer has been controversial due to concern, based almost exclusively on in vitro and rodent data, that isoflavones may be contraindicated for breast cancer patients and for women at high risk of this disease.[107] Although a very detailed analysis is required to fully explore this complex topic, the key findings are summarized below.

At high concentrations, the isoflavone genistein inhibits the growth of estrogen-sensitive breast cancer cells in vitro, whereas at lower more physiologic concentrations, growth is stimulated.[108] More importantly, isoflavone-containing products have been found to stimulate the growth of mammary tumors in ovariectomized athymic mice implanted with estrogen-sensitive breast cancer cells.[109] Stimulation appears to result primarily from exposure to the isoflavone genistein.[110] Interestingly, in this particular animal model, more highly processed soy products stimulate tumor growth to a greater extent than less processed ones, despite containing similar amounts of genistein.[111] In fact, soy flour, the least processed product to be evaluated, does not result in tumor stimulation.

In contrast to the animal data, the pertinent human data suggest that isoflavones do not exert stimulatory effects on breast tissue. Also, in contrast to the effects of combined hormone therapy, isoflavones do not increase breast tissue density or breast cell proliferation in vivo, both of which are markers of breast cancer risk.[112] Combined menopausal hormone therapy, which increases breast cancer risk, increases breast cell proliferation fourfold within just 12 weeks.[113, 114]

The lack of harmful effects noted in the clinical studies is consistent with the results from three epidemiologic investigations that have examined the impact of soyfood intake on the prognosis of breast cancer patients. In one, neither soy nor isoflavone intake was related to the disease-free survival of Chinese breast cancer patients over the 5.2 year follow-up period.[115] In this study, of the 1,001 (total cohort included 1,459 subjects) patients for whom data on receptor status was available, approximately 63 percent were estrogen receptor-positive.

The second epidemiologic study, which was recently published in the ***Journal of the American Medical Association (JAMA)***, is the first specifically designed to examine the soy and breast cancer controversy.[116] Data from the Shanghai Breast Cancer Survival Study, a population-based cohort study of breast cancer survivors, were analyzed to investigate the effect of soy intake after diagnosis on breast cancer prognosis.[117] During the median follow-up period of approximately 3.9 years, the hazard ratio associated with the highest quartile of soy protein intake was 0.71 for total mortality and 0.68 for recurrence compared with the lowest quartile of intake. In fact, in this study, high soy intake was as protective as tamoxifen use. In an editorial accompanying the *JAMA* article, researchers from the National Cancer Institute and Fred Hutchinson Research Center in Seattle remarked that, "Patients with breast cancer can be assured that enjoying a soy latte or indulging in pad thai with tofu causes no harm and, when consumed in plentiful amounts, may reduce risk of disease recurrence."[118]

*According to the American Cancer Society, breast cancer patients can consume up to three servings of soyfoods daily.*

In the third study, which was conducted in the United States and involved nearly 2,000 breast cancer patients, over the six year follow-up period, results suggested that isoflavone intake may have improved prognosis overall and in particular among those women taking tamoxifen.[119] The findings of these three epidemiologic studies are consistent with the position of the American Cancer Society that breast cancer patients can safely consume up to three servings of traditional soyfoods daily.[120] Nevertheless, breast cancer patients should discuss any dietary changes with their primary healthcare provider.

For information about soy and heart health, please reference the Soy Connection's Soy & Heart Health fact sheet.

## Summary and Conclusions

Epidemiologic and clinical data suggest that soyfoods can make important contributions to the health of women, and particularly postmenopausal women. More specifically, the results from this research suggest that isoflavone-containing products help alleviate hot flashes and perhaps reduce bone loss although the latter is very speculative. Further, the data overall suggest that soyfoods do not pose a risk to breast cancer patients or women at high risk of this disease and therefore can be safely consumed by all women at any point in their lifetime.

### Sources of Soy Protein

| Soyfood | Serving size | Grams of soy protein |
|---|---|---|
| Fortified soymilk | 1 cup | 6-7 |
| Soy cereal | 1 ¼ cup | 7 |
| Soy yogurt, vanilla | 1 cup | 6 |
| Soy breakfast patty | 2 patties | 11 |
| Soy bar | 1 bar | 14 |
| Soy chips | 1 bag | 7 |
| Soy nut butter | 2 Tbsp | 7 |
| Soy nuts, roasted, unsalted | ¼ cup | 11 |
| Tofu | ½ cup | 10 |
| Edamame | ½ cup | 11 |
| Soy burger | 1 patty | 13-14 |
| Soy pasta | ½ cup (cooked) | 13 |
| Soy pudding | ½ cup | 6 |

## References


1. Messina M, Lane B. Soy protein, soybean isoflavones, and coronary heart disease risk: Where do we stand? Future Lipidology. 2007;2:55-74.
2. Ma DF, Qin LQ, Wang PY, Katoh R. Soy isoflavone intake increases bone mineral density in the spine of menopausal women: Meta-analysis of randomized controlled trials. Clin Nutr. 2007 Dec 4.
3. Howes LG, Howes JB, Knight DC. Isoflavone therapy for menopausal flushes: a systematic review and meta-analysis. Maturitas. 2006 Oct 20;55:203-11.
4. Gollschewski S, Kitto S, Anderson D, Lyons-Wall P. Women's perceptions and beliefs about the use of complementary and alternative medicines during menopause. Complement Ther Med. 2008 Jun;16:163-8.
5. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. JAMA. 2002 Jul 17;288:321-33.
6. Helferich WG, Andrade JE, Hoagland MS. Phytoestrogens and breast cancer: a complex story. Inflammopharmacology. 2008 Oct;16:219-26.
7. Franke AA, Custer LJ, Wang W, Shi CY. HPLC analysis of isoflavonoids and other phenolic agents from foods and from human fluids. Proc Soc Exp Biol Med. 1998;217:263-73.
8. Messina M, Nagata C, Wu AH. Estimated Asian adult soy protein and isoflavone intakes. Nutr Cancer. 2006;55:1-12.
9. Horn-Ross PL, John EM, Canchola AJ, Stewart SL, Lee MM. Phytoestrogen intake and endometrial cancer risk. J Natl Cancer Inst. 2003 Aug 6;95:1158-64.
10. Goodman-Gruen D, Kritz-Silverstein D. Usual dietary isoflavone intake is associated with cardiovascular disease risk factors in postmenopausal women. J Nutr. 2001 Apr;131:1202-6.
11. 2004Q-0151: Qualified Health Claim (QHC): Soy Protein and Cancer (http://www.fda.gov/ohrms/dockets/dockets/04q0151/04q0151.htm). [cited March 14, 2004]; Available from: http://www.fda.gov/ohrms/dockets/dockets/04q0151/04q0151.htm
12. de Kleijn MJ, van der Schouw YT, Wilson PW, Adlercreutz H, Mazur W, Grobbee DE, Jacques PF. Intake of dietary phytoestrogens is low in postmenopausal women in the United States: the Framingham study (1-4). J Nutr. 2001 Jun;131:1826-32.
13. van Erp-Baart MA, Brants HA, Kiely M, Mulligan A, Turrini A, Sermoneta C, Kilkkinen A, Valsta LM. Isoflavone intake in four different European countries: the VENUS approach. Br J Nutr. 2003 Jun;89 Suppl 1:S25-30.
14. van der Schouw YT, Kreijkamp-Kaspers S, Peeters PH, Keinan-Boker L, Rimm EB, Grobbee DE. Prospective study on usual dietary phytoestrogen intake and cardiovascular disease risk in Western women. Circulation. 2005 Feb 1;111:465-71.
15. Boker LK, Van der Schouw YT, De Kleijn MJ, Jacques PF, Grobbee DE, Peeters PH. Intake of dietary phytoestrogens by Dutch women. J Nutr. 2002 Jun;132:1319-28.
16. Murphy PA, Barua K, Hauck CC. Solvent extraction selection in the determination of isoflavones in soy foods. J Chromatogr B Analyt Technol Biomed Life Sci. 2002 Sep 25;777:129-38.
17. Kuiper GG, Carlsson B, Grandien K, Enmark E, Haggblad J, Nilsson S, Gustafsson JA. Comparison of the ligand binding specificity and transcript tissue distribution of estrogen receptors alpha and beta. Endocrinology. 1997 Mar;138:863-70.
18. Kuiper GG, Lemmen JG, Carlsson B, Corton JC, Safe SH, van der Saag PT, van der Burg B, Gustafsson JA. Interaction of estrogenic chemicals and phytoestrogens with estrogen receptor beta. Endocrinology. 1998 Oct;139:4252-63.
19. Nagata C, Iwasa S, Shiraki M, Ueno T, Uchiyama S, Urata K, Sahashi Y, Shimizu H. Associations among maternal soy intake, isoflavone levels in urine and blood samples, and maternal and umbilical hormone concentrations (Japan). Cancer Causes Control. 2006 Nov;17:1107-13.
20. An J, Tzagarakis-Foster C, Scharschmidt TC, Lomri N, Leitman DC. Estrogen Receptor beta -Selective Transcriptional Activity and Recruitment of Coregulators by Phytoestrogens. J Biol Chem. 2001 May 25;276:17808-14.
21. Margeat E, Bourdoncle A, Margueron R, Poujol N, Cavailles V, Royer C. Ligands Differentially Modulate the Protein Interactions of the Human Estrogen Receptors alpha and beta. J Mol Biol. 2003 Feb 7;326:77-92.
22. Kostelac D, Rechkemmer G, Briviba K. Phytoestrogens modulate binding response of estrogen receptors alpha and beta to the estrogen response element. J Agric Food Chem. 2003 Dec 17;51:7632-5.
23. Pike AC, Brzozowski AM, Hubbard RE, Bonn T, Thorsell AG, Engstrom O, Ljunggren J, Gustafsson JA, Carlquist M. Structure of the ligand-binding domain of oestrogen receptor beta in the presence of a partial agonist and a full antagonist. EMBO J. 1999 Sep 1;18:4608-18.
24. Brzezinski A, Adlercreutz H, Shaoul R, Rösler R, Shmueli A, Tanos V, Schenker JG. Short-term effect of phytoestrogen-rich diet on postmenopausal women. Menopause. 1997;4:89-94.
25. Diel P, Geis RB, Caldarelli A, Schmidt S, Leschowsky UL, Voss A, Vollmer G. The differential ability of the phytoestrogen genistein and of estradiol to induce uterine weight and proliferation in the rat is associated with a substance specific modulation of uterine gene expression. Mol Cell Endocrinol. 2004 Jun 30;221:21-32.
26. Yildiz MF, Kumru S, Godekmerdan A, Kutlu S. Effects of raloxifene, hormone therapy, and soy isoflavone on serum high-sensitive C-reactive protein in postmenopausal women. Int J Gynaecol Obstet. 2005 Aug;90:128-33.
27. Jordan VC. Selective estrogen receptor modulation: concept and consequences in cancer. Cancer Cell. 2004 Mar;5:207-13.
28. Ho JY, Chen MJ, Sheu WH, Yi YC, Tsai AC, Guu HF, Ho ES. Differential effects of oral conjugated equine estrogen and transdermal estrogen on atherosclerotic vascular disease risk markers and endothelial function in healthy postmenopausal women. Hum Reprod. 2006 Oct;21:2715-20.
29. Lakoski SG, Brosnihan B, Herrington DM. Hormone therapy, C-reactive protein, and progression of atherosclerosis: data from the Estrogen Replacement on Progression of Coronary Artery Atherosclerosis (ERA) trial. Am Heart J. 2005 Nov;150:907-11.
30. Helgason S, Damber JE, Damber MG, von Schoultz B, Selstam G, Sodergard R. A comparative longitudinal study on sex hormone binding globulin capacity during estrogen replacement therapy. Acta Obstet Gynecol Scand. 1982;61:97-100.
31. Serin IS, Ozcelik B, Basbug M, Aygen E, Kula M, Erez R. Long-term effects of continuous oral and transdermal estrogen replacement therapy on sex hormone binding globulin and free testosterone levels. Eur J Obstet Gynecol Reprod Biol. 2001 Dec 1;99:222-5.
32. Reid IR, Eastell R, Fogelman I, Adachi JD, Rosen A, Netelenbos C, Watts NB, Seeman E, Ciaccia AV, Draper MW. A comparison of the effects of raloxifene and conjugated equine estrogen on bone and lipids in healthy postmenopausal women. Arch Intern Med. 2004 Apr 26;164:871-9.
33. Shulman LP. Effects of progestins in different hormone replacement therapy formulations on estrogen-induced lipid changes in postmenopausal women. Am J Cardiol. 2002 Jun 20;89:47E-54E; discussion E-5E.
34. Marqusee E, Braverman LE, Lawrence JE, Carroll JS, Seely EW. The effect of droloxifene and estrogen on thyroid function in postmenopausal women. J Clin Endocrinol Metab. 2000 Nov;85:4407-10.
35. Abech DD, Moratelli HB, Leite SC, Oliveira MC. Effects of estrogen replacement therapy on pituitary size, prolactin and thyroid-stimulating hormone concentrations in menopausal women. Gynecol Endocrinol. 2005 Oct;21:223-6.
36. Davies GC, Huster WJ, Shen W, Mitlak B, Plouffe L, Jr., Shah A, Cohen FJ. Endometrial response to raloxifene compared with placebo, cyclical hormone replacement therapy, and unopposed estrogen in postmenopausal women. Menopause. 1999 Fall;6:188-95.
37. Meuwissen JH, van Langen H. Monitoring endometrial thickness during estrogen replacement therapy with vaginosonography. Radiology. 1992 Apr;183:284.
38. Kaari C, Haidar MA, Junior JM, Nunes MG, Quadros LG, Kemp C, Stavale JN, Baracat EC. Randomized clinical trial comparing conjugated equine estrogens and isoflavones in postmenopausal women: a pilot study. Maturitas. 2006 Jan 10;53:49-58.
39. D'Anna R, Baviera G, Corrado F, Cancellieri F, Crisafulli A, Squadrito F. The effect of the phytoestrogen genistein and hormone replacement therapy on homocysteine and C-reactive protein level in postmenopausal women. Acta Obstet Gynecol Scand. 2005 May;84:474-7.
40. Garrido A, De la Maza MP, Hirsch S, Valladares L. Soy isoflavones affect platelet thromboxane A2 receptor density but not plasma lipids in menopausal women. Maturitas. 2006 Jun 20;54:270-6.
41. Khaodhiar L, Ricciotti HA, Li L, Pan W, Schickel M, Zhou J, Blackburn GL. Daidzein-rich isoflavone aglycones are potentially effective in reducing hot flashes in menopausal women. Menopause. 2007 Jul 18;Publish Ahead of Print.
42. Hall WL, Vafeiadou K, Hallund J, Bugel S, Reimann M, Koebnick C, Zunft HJ, Ferrari M, Branca F, et al. Soy-isoflavone-enriched foods and markers of lipid and glucose metabolism in postmenopausal women: interactions with genotype and equol production. Am J Clin Nutr. 2006 Mar;83:592-600.
43. Katz DL, Evans MA, Njike VY, Hoxley ML, Nawaz H, Comerford BP, Sarrel PM. Raloxifene, soy phytoestrogens and endothelial function in postmenopausal women. Climacteric. 2007 Dec;10:500-7.
44. Cheng G, Wilczek B, Warner M, Gustafsson JA, Landgren BM. Isoflavone treatment for acute menopausal symptoms. Menopause. 2007 May-Jun;14:468-73.
45. Bruce B, Messina M, Spiller GA. Isoflavone supplements do not affect thyroid function in iodine-replete postmenopausal women. J Med Food. 2003 Winter;6:309-16.
46. Marini H, Minutoli L, Polito F, Bitto A, Altavilla D, Atteritano M, Gaudio A, Mazzaferro S, Frisina A, et al. Effects of the phytoestrogen genistein on bone metabolism in osteopenic postmenopausal women: a randomized trial. Ann Intern Med. 2007 Jun 19;146:839-47.
47. Sammartino A, Di Carlo C, Mandato VD, Bifulco G, Di Stefano M, Nappi C. Effects of genistein on the endometrium: ultrasonographic evaluation. Gynecol Endocrinol. 2003 Feb;17:45-9.
48. Sarkar FH, Li Y. Soy isoflavones and cancer prevention. Cancer Invest. 2003;21:744-57.
49. Fang N, Yu S, Badger TM. Comprehensive phytochemical profile of soy protein isolate. J Agric Food Chem. 2004 Jun 16;52:4012-20.
50. Kronenberg F. Hot flashes: epidemiology and physiology. Ann N Y Acad Sci. 1990;592:52-86; discussion 123-33.
51. Berg G, Gottwall T, Hammar M, Lindgren R, Gottgall T. Climacteric symptoms among women aged 60-62 in Linkoping, Sweden, in 1986. Maturitas. 1988 Oct;10:193-9.
52. Rodstrom K, Bengtsson C, Lissner L, Milsom I, Sundh V, Bjorkelund C. A longitudinal study of the treatment of hot flushes: the population study of women in Gothenburg during a quarter of a century. Menopause. 2002 May-Jun;9:156-61.
53. Adlercreutz H, Hamalainen E, Gorbach S, Goldin B. Dietary phyto-oestrogens and the menopause in Japan. Lancet. 1992 May 16;339:1233.
54. Gold EB, Sternfeld B, Kelsey JL, Brown C, Mouton C, Reame N, Salamone L, Stellato R. Relation of demographic and lifestyle factors to symptoms in a multi- racial/ethnic population of women 40-55 years of age. Am J Epidemiol. 2000 Sep 1;152:463-73.
55. Maki PM, Rubin LH, Fornelli D, Drogos L, Banuvar S, Shulman LP, Geller SE. Effects of botanicals and combined hormone therapy on cognition in postmenopausal women. Menopause. 2009 Jul 31.
56. D'Anna R, Cannata ML, Atteritano M, Cancellieri F, Corrado F, Baviera G, Triolo O, Antico F, Gaudio A, et al. Effects of the phytoestrogen genistein on hot flushes, endometrium, and vaginal epithelium in postmenopausal women: a 1-year randomized, double-blind, placebo-controlled study. Menopause. 2007 Jul-Aug;14:648-55.
57. D'Anna R, Cannata ML, Marini H, Atteritano M, Cancellieri F, Corrado F, Triolo O, Rizzo P, Russo S, et al. Effects of the phytoestrogen genistein on hot flushes, endometrium, and vaginal epithelium in postmenopausal women: a 2-year randomized, double-blind, placebo-controlled study. Menopause. 2008 Nov 20.
58. Nahas EA, Nahas-Neto J, Orsatti FL, Carvalho EP, Oliveira ML, Dias R. Efficacy and safety of a soy isoflavone extract in postmenopausal women: A randomized, double-blind, and placebo-controlled study. Maturitas. 2007 Oct 1.
59. Messina M, Hughes C. Efficacy of soyfoods and soybean isoflavone supplements for alleviating menopausal symptoms is positively related to initial hot flush frequency. J Med Food. 2003 Spring;6:1-11.
60. Jacobs A, Wegewitz U, Sommerfeld C, Grossklaus R, Lampen A. Efficacy of isoflavones in relieving vasomotor menopausal symptoms - A systematic review. Mol Nutr Food Res. 2009 Sep;53:1084-97.
61. Lethaby A, Brown J, Marjoribanks J, Kronenberg F, Roberts H, Eden J. Phytoestrogens for vasomotor menopausal symptoms. Cochrane Database Syst Rev. 2007:CD001395.
62. Wiseman H, Casey K, Bowey EA, Duffy R, Davies M, Rowland IR, Lloyd AS, Murray A, Thompson R, Clarke DB. Influence of 10 wk of soy consumption on plasma concentrations and excretion of isoflavonoids and on gut microflora metabolism in healthy adults. Am J Clin Nutr. 2004 Sep;80:692-9.




*Continued on back page*

*References continued from inside page*


63. Rowland IR, Wiseman H, Sanders TA, Adlercreutz H, Bowey EA. Interindividual variation in metabolism of soy isoflavones and lignans: influence of habitual diet on equol production by the gut microflora. Nutr Cancer. 2000;36:27-32.
64. Rowland I, Faughnan M, Hoey L, Wahala K, Williamson G, Cassidy A. Bioavailability of phyto-oestrogens. Br J Nutr. 2003 Jun;89 Suppl 1:S45-58.
65. Williamson-Hughes PS, Flickinger BD, Messina MJ, Empie MW. Isoflavone supplements containing predominantly genistein reduce hot flash symptoms: a critical review of published studies. Menopause. 2006 Aug 22.
66. Weaver CM, Martin BR, Jackson GS, McCabe GP, Nolan JR, McCabe LD, Barnes S, Reinwald S, Boris ME, Peacock M. Antiresorptive effects of phytoestrogen supplements compared with estradiol or risedronate in postmenopausal women using (41)Ca methodology. J Clin Endocrinol Metab. 2009 Oct;94:3798-805.
67. Messina M, Watanabe S, Setchell KD. Report on the 8th International Symposium on the Role of Soy in Health Promotion and Chronic Disease Prevention and Treatment. J Nutr. 2009 Apr;139:796S-802S.
68. Butt DA, Deng LY, Lewis JE, Lock M. Minimal decrease in hot flashes desired by postmenopausal women in family practice. Menopause. 2007 Mar-Apr;14:203-7.
69. Finkelstein JS, Brockwell SE, Mehta V, Greendale GA, Sowers MR, Ettinger B, Lo JC, Johnston JM, Cauley JA, et al. Bone Mineral Density Changes During the Menopause Transition in a Multi-Ethnic Cohort of Women. J Clin Endocrinol Metab. 2007 Dec 26.
70. Brandi ML, Gennari C. Ipriflavone: new insights into its mechanisms of action on bone remodeling. Calcif Tissue Int. 1993 Feb;52:151-2.
71. Ross PD, Norimatsu H, Davis JW, Yano K, Wasnich RD, Fujiwara S, Hosoda Y, Melton LJ. A comparison of hip fracture incidence among native Japanese, Japanese Americans, and American Caucasians. Am J Epidemiol. 1991 Apr 15;133:801-9.
72. Chin K, Evans MC, Cornish J, Cundy T, Reid IR. Differences in hip axis and femoral neck length in premenopausal women of Polynesian, Asian and European origin. Osteoporos Int. 1997;7:344-7.
73. Cummings SR, Cauley JA, Palermo L, Ross PD, Wasnich RD, Black D, Faulkner KG. Racial differences in hip axis lengths might explain racial differences in rates of hip fracture. Study of Osteoporotic Fractures Research Group. Osteoporos Int. 1994;4:226-9.
74. Aoyagi K, Ross PD, Davis JW, Wasnich RD, Hayashi T, Takemoto T. Falls among community-dwelling elderly in Japan. J Bone Miner Res. 1998;13:1468-74.
75. Davis JW, Ross PD, Nevitt MC, Wasnich RD. Incidence rates of falls among Japanese men and women living in Hawaii. J Clin Epidemiol. 1997;50:589-94.
76. Ross PD, He Y, Yates AJ, Coupland C, Ravn P, McClung M, Thompson D, Wasnich RD. Body size accounts for most differences in bone density between Asian and Caucasian women. The EPIC (Early Postmenopausal Interventional Cohort) Study Group. Calcif Tissue Int. 1996;59:339-43.
77. Russell-Aulet M, Wang J, Thornton JC, Colt EW, Pierson RN, Jr. Bone mineral density and mass in a cross-sectional study of white and Asian women. J Bone Miner Res. 1993;8:575-82.
78. Nomura A, Wasnich RD, Heilbrun LK, Ross PD, Davis JW. Comparison of bone mineral content between Japan-born and US-born Japanese subjects in Hawaii. Bone Miner. 1989 May;6:213-23.
79. Ross PD, Fujiwara S, Huang C, Davis JW, Epstein RS, Wasnich RD, Kodama K, Melton LJ, 3rd. Vertebral fracture prevalence in women in Hiroshima compared to Caucasians or Japanese in the US. Int J Epidemiol. 1995;24:1171-7.
80. Lau EM, Chan HH, Woo J, Lin F, Black D, Nevitt M, Leung PC. Normal ranges for vertebral height ratios and prevalence of vertebral fracture in Hong Kong Chinese: a comparison with American Caucasians. J Bone Miner Res. 1996;11:1364-8.
81. Dennison E, Yoshimura N, Hashimoto T, Cooper C. Bone loss in Great Britain and Japan: a comparative longitudinal study. Bone. 1998;23:379-82.
82. Tsai K, Huang K, Chieng P, Su C. Bone mineral density of normal Chinese women in Taiwan. Calcif Tissue Inter. 1991;48:161-6.
83. Tsai K, Twu S, Chieng P, Yang R, Lee T. Prevalence of vertebral fractures in chinese men and women in urban Taiwanese communities. Calcif Tissue Int. 1996;59:249-53.
84. Zhang X, Shu XO, Li H, Yang G, Li Q, Gao YT, Zheng W. Prospective cohort study of soy food consumption and risk of bone fracture among postmenopausal women. Arch Intern Med. 2005 Sep 12;165:1890-5.
85. Koh WP, Wu AH, Wang R, Ang LW, Heng D, Yuan JM, Yu MC. Gender-specific associations between soy and risk of hip fracture in the Singapore Chinese Health Study. Am J Epidemiol. 2009 Oct 1;170:901-9.
86. Potter SM, Baum JA, Teng H, Stillman RJ, Shay NF, Erdman JW, Jr. Soy protein and isoflavones: their effects on blood lipids and bone density in postmenopausal women. Am J Clin Nutr. 1998;68:1375S-9S.
87. Atmaca A, Kleerekoper M, Bayraktar M, Kucuk O. Soy isoflavones in the management of postmenopausal osteoporosis. Menopause. 2008 Feb 14.
88. Messina M, Ho S, Alekel DL. Skeletal benefits of soy isoflavones: a review of the clinical trial and epidemiologic data. Curr Opin Clin Nutr Metab Care. 2004 Dec;7:649-58.
89. Ma DF, Qin LQ, Wang PY, Katoh R. Soy isoflavone intake inhibits bone resorption and stimulates bone formation in menopausal women: meta-analysis of randomized controlled trials. Eur J Clin Nutr. 2007 Mar 28.
90. Liu J, Ho SC, Su YX, Chen WQ, Zhang CX, Chen YM. Effect of long-term intervention of soy isoflavones on bone mineral density in women: A meta-analysis of randomized controlled trials. Bone. 2009 Jan 3.
91. Marini H, Bitto A, Altavilla D, Burnett BP, Polito F, Di Stefano V, Minutoli L, Atteritano M, Levy RM, et al. Breast safety and efficacy of genistein aglycone for postmenopausal bone loss: a follow-up study. J Clin Endocrinol Metab. 2008 Dec;93:4787-96.
92. Lydeking-Olsen E, Beck-Jensen JE, Setchell KD, Holm-Jensen T. Soymilk or progesterone for prevention of bone loss: A 2 year randomized, placebo-controlled trial. Eur J Nutr. 2004 Apr 14;43:246-57.
93. Brink E, Coxam V, Robins S, Wahala K, Cassidy A, Branca F. Long-term consumption of isoflavone-enriched foods does notaffect bone mineral density, bone metabolism, or hormonal status inearly postmenopausal women: a randomized, double-blind, placebocontrolled study. Am J Clin Nutr. 2008;87:761-70.
94. Kenny AM, Mangano KM, Abourizk RH, Bruno RS, Anamani DE, Kleppinger A, Walsh SJ, Prestwood KM, Kerstetter JE. Soy proteins and isoflavones affect bone mineral density in older women: a randomized controlled trial. Am J Clin Nutr. 2009 Jul;90:234-42.
95. Vupadhyayula PM, Gallagher JC, Templin T, Logsdon SM, Smith LM. Effects of soy protein isolate on bone mineral density and physical performance indices in postmenopausal women-a 2-year randomized, double-blind, placebo-controlled trial. Menopause. 2009 Jan 21.
96. Alekel DL, Van Loan MD, Koehler KJ, Hanson LN, Stewart JW, Hanson KB, Kurzer MS, Peterson CT. The Soy Isoflavones for Reducing Bone Loss (SIRBL) Study: a 3-y randomized controlled trial in postmenopausal women. Am J Clin Nutr. 2009 Nov 11.
97. Rand WM, Pellett PL, Young VR. Meta-analysis of nitrogen balance studies for estimating protein requirements in healthy adults. Am J Clin Nutr. 2003 Jan;77:109-27.
98. Darling AL, Millward DJ, Torgerson DJ, Hewitt CE, Lanham-New SA. Dietary protein and bone health: a systematic review and meta-analysis. Am J Clin Nutr. 2009 Nov 4.
99. Zhao Y, Martin BR, Weaver CM. Calcium Bioavailability of Calcium Carbonate Fortified Soymilk Is Equivalent to Cow's Milk in Young Women. J Nutr. 2005 Oct;135:2379-82.
100. Wu AH, Yu MC, Tseng CC, Pike MC. Epidemiology of soy exposures and breast cancer risk. Br J Cancer. 2008 Jan 15;98:9-14.
101. Lamartiniere CA, Zhao YX, Fritz WA. Genistein: mammary cancer chemoprevention, in vivo mechanisms of action, potential for toxicity and bioavailability in rats. J Women's Cancer. 2000;2:11-9.
102. Shu XO, Jin F, Dai Q, Wen W, Potter JD, Kushi LH, Ruan Z, Gao YT, Zheng W. Soyfood Intake during Adolescence and Subsequent Risk of Breast Cancer among Chinese Women. Cancer Epidemiol Biomarkers Prev. 2001 May;10:483-8.
103. Wu AH, Yu MC, Tseng CC, Stanczyk FZ, Pike MC. Dietary patterns and breast cancer risk in Asian American women. Am J Clin Nutr. 2009 Feb 11.
104. Peng JH, Zhang F, Zhang HX, Fan HY. Prepubertal octylphenol exposure up-regulate BRCA1 expression, down-regulate ERalpha expression and reduce rat mammary tumorigenesis. Cancer Epidemiol. 2009 Jul;33:51-5.
105. Messina M, Hilakivi-Clarke L. Early intake appears to be the key to the proposed protective effects of soy intake against breast cancerNutr Cancer. 2009;61:792-8.
106. Russo J, Mailo D, Hu YF, Balogh G, Sheriff F, Russo IH. Breast differentiation and its implication in cancer prevention. Clin Cancer Res. 2005 Jan 15;11:931s-6s.
107. Messina M, McCaskill-Stevens W, Lampe JW. Addressing the soy and breast cancer relationship: review, commentary, and workshop proceedings. J Natl Cancer Inst. 2006 Sep 20;98:1275-84.
108. Hsieh CY, Santell RC, Haslam SZ, Helferich WG. Estrogenic effects of genistein on the growth of estrogen receptor- positive human breast cancer (MCF-7) cells in vitro and in vivo. Cancer Res. 1998;58:3833-8.
109. Allred CD, Ju YH, Allred KF, Chang J, Helferich WG. Dietary genistin stimulates growth of estrogen-dependent breast cancer tumors similar to that observed with genistein. Carcinogenesis. 2001 Oct;22:1667-73.
110. Ju YH, Fultz J, Allred KF, Doerge DR, Helferich WG. Effects of dietary daidzein and its metabolite, equol, at physiological concentrations on the growth of estrogen-dependent human breast cancer (MCF-7) tumors implanted in ovariectomized athymic mice. Carcinogenesis. 2006 Apr;27:856-63.
111. Allred CD, Twaddle NC, Allred KF, Goeppinger TS, Churchwell MI, Ju YH, Helferich WG, Doerge DR. Soy processing affects metabolism and disposition of dietary isoflavones in ovariectomized BALB/c mice. J Agric Food Chem. 2005 Nov 2;53:8542-50.
112. Messina MJ, Wood CE. Soy isoflavones, estrogen therapy, and breast cancer risk: Analysis and commentary. Nutr J. 2008 Jun 3;7:17.
113. Conner P, Skoog L, Soderqvist G. Breast epithelial proliferation in postmenopausal women evaluated through fine-needle-aspiration cytology. Climacteric. 2001 Mar;4:7-12.
114. Conner P, Soderqvist G, Skoog L, Graser T, Walter F, Tani E, Carlstrom K, von Schoultz B. Breast cell proliferation in postmenopausal women during HRT evaluated through fine needle aspiration cytology. Breast Cancer Res Treat. 2003 Mar;78:159-65.
115. Boyapati SM, Shu XO, Ruan ZX, Dai Q, Cai Q, Gao YT, Zheng W. Soyfood intake and breast cancer survival: a followup of the Shanghai Breast Cancer Study. Breast Cancer Res Treat. 2005 Jul;92:11-7.
116. Messina M, Watanabe S, Setchell KD. Report on the 8th International Symposium on the Role of Soy in Health Promotion and Chronic Disease Prevention and Treatment. J Nutr. 2009 Feb 18.
117. Shu XO, Zheng Y, Cai H, Gu K, Chen Z, Zheng W, Lu W. Soy food intake and breast cancer survival. JAMA. 2009 Dec 9;302:2437-43.
118. Ballard-Barbash R, Neuhouser ML. Challenges in design and interpretation of observational research on health behaviors and cancer survival. JAMA. 2009 Dec 9;302:2483-4.
119. Guha N, Kwan ML, Quesenberry CP, Jr., Weltzien EK, Castillo AL, Caan BJ. Soy isoflavones and risk of cancer recurrence in a cohort of breast cancer survivors: the Life After Cancer Epidemiology study. Breast Cancer Res Treat. 2009 Feb 17.
120. Doyle C, Kushi LH, Byers T, Courneya KS, Demark-Wahnefried W, Grant B, McTiernan A, Rock CL, Thompson C, et al. Nutrition and physical activity during and after cancer treatment: an american cancer society guide for informed choices. CA Cancer J Clin. 2006 Nov-Dec;56:323-53.


UNITED SOYBEAN BOARD
*Making Your Checkoff Pay Off.*

The United Soybean Board (USB) is a farmer-led organization comprised of 68 farmer-directors. Working with independent academic researchers affiliated with the National Institutes of Health (NIH) and academic institutions, USB has invested millions of dollars into health and nutrition research related to soy. Soybean farmers take pride in producing one of the healthiest food crops in the world. To access healthy soy recipes and more nutrition information, please visit SoyConnection.com.

0322-012010-2500