Soy Connection Fact Sheet

SOY + WOMEN'S HEALTH

Soyfoods offer health benefits for all consumers, but studies show that postmenopausal women may reap particular benefits. This fact sheet discusses recent research into the benefits and safety of soy for women, from heart disease to hot flashes.

Introduction

Traditional soyfoods such as tofu and miso have been widely consumed for centuries in many Asian countries. Health-conscious individuals in Western countries have consumed these foods for decades. Over the past 25 years, increased numbers of non-Asians have incorporated soy into their diets because of purported health benefits. Soyfoods hold particular appeal for postmenopausal women because they are uniquely rich sources of isoflavones, one type of phytoestrogen.

Isoflavones exhibit estrogen-like effects under certain experimental conditions and are posited to reduce risk of coronary heart disease (CHD),[1] osteoporosis,[2] certain forms of cancer,[3] and alleviate menopause-related hot flashes.[4] 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.[5]

However, despite interest in the health benefits of isoflavones, these soybean constituents are not without controversy. Their estrogen-like effects have raised concern that they possess some of the same undesirable properties as the hormone therapy. Most notable in this regard is the concern

that soyfoods may adversely impact the prognosis of women with breast cancer and increase risk of high-risk women developing breast cancer.[6] This concern is without scientific support and will be discussed in this brochure. Soyfoods are a unique dietary source of isoflavones, a phytoestrogen that may offer heart health benefits and may help alleviate hot flashes during menopause.

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

Overview of Isoflavones

Isoflavones have a limited distribution in nature such that diets that do not include soyfoods are almost devoid of these compounds.[7] Isoflavone intake among older individuals in Japan[8] and Shanghai[8] are about 30 to 50 milligrams per day (mg/d), whereas intake is less than 3 mg/d in the United States, Canada and Europe.[9–15] Isoflavones primarily occur in soybeans as glycosides,[16] but upon ingestion, the sugar is hydrolyzed thereby allowing absorption to occur.[17] In fermented soyfoods such as miso, tempeh and natto, substantial amounts of the isoflavones occur as aglycones due to bacterial hydrolysis. The three isoflavones, genistein, daidzein and glycitein and their respective glycosides account for approximately 50, 40 and 10%, respectively, of the total isoflavone content of the soybean.[16]

Each gram of soy protein in soybeans and traditional Asian soyfoods is associated with approximately 3.5 mg of isoflavones.[8] Consequently, one serving of a traditional soyfood, such as 3 to 4 ounces of tofu or 1 cup of soymilk, typically provides about 25 mg of isoflavones.

Isoflavones bind to both estrogen receptors (ER) – ERα and ERβ[18,19] – and are able to exert estrogen-like effects under certain experimental conditions; hence, their classification as phytoestrogens. However, whereas estrogen binds to and activates ERα and ERβ equally, isoflavones preferentially bind to and activate ERβ.[20–23] This difference in binding and activation between isoflavones and estrogen is important because the two ERs have different tissue distributions, and when activated, can have different and sometimes even opposite physiological effects. This appears to be the case in the breast, where ERβ activation is thought to inhibit the proliferative effects of ERα activation.[24,25] In fact, recent findings implicate ERβ-specific agonists with having growth-inhibitory effects in several cancer models.[26]

The preference of isoflavones for ERβ is the primary reason that isoflavones are viewed as capable of exerting tissue-specific effects and classified as selective estrogen receptor modulators (SERMs).[27–29] In tissues that possess ERs, SERMs exert estrogen-like effects in some tissues but no effects or antiestrogenic effects in others.

Hot Flashes

Hot flashes are the most common reason given by women seeking treatment for menopausal symptoms. For most women who experience them, hot flashes begin prior to menopause. Ten to 15 percent of these women experience hot flashes that are severe and frequent.[30]

The low incidence of hot flashes among native Japanese women helped raise initial speculation that isoflavones could be useful in their prevention.[31] Since 1995, more than 50 clinical trials have examined the impact of isoflavones from different sources on the alleviation of menopause-related hot flashes. Most studies intervened with supplements rather than soyfoods to enhance compliance and to reduce the complexity of study design. The results of these trials have produced inconsistent results. However, with one exception, analyses of the clinical research have failed to consider the importance of sub-analyzing the data according to the type of isoflavone supplement employed based on genistein content, which is the isoflavone considered to be most potent.[32]

This exception is a systematic review and meta-analysis published in 2012, which included 17 and 19 trials, respectively, all of which intervened with isoflavone supplements derived from soy.[32] The meta-analysis of the data on hot flash frequency, which included 13 studies involving 1,196 women, found isoflavones were consistently efficacious, reducing the number of hot flashes per day by about 21 percent more than the reduction in the placebo group ($p< 0.00001$). Similarly, in the nine trials involving 988 women that evaluated hot flash severity, isoflavones reduced symptoms by about 26 percent more than the reduction in the placebo group ($p<0.001$). When considering the combined effect of the placebo and isoflavones, the overall reduction in frequency and severity was approximately 50 percent.

Isoflavone Content of Soyfoods

SOYFOOD	SERVING SIZE	TOTAL (MG) ISOFALVONE/SERVING
Miso	1 tbsp	7
Soybeans, Green, Cooked	½ cup	50
Soybeans, Black, Cooked	½ cup	40
Soybeans, Yellow, Cooked	½ cup	78
Soybeans, Roasted, Plain	¼ cup	78
Soymilk, Plain, Unfortified	1 cup	10
Soymilk, Plain, Fortified	1 cup	43
Soy Flour, Defatted	¼ cup	42
Soy Flour, Full-Fat	¼ cup	33
Soy Flour, Low-Fat	¼ cup	50
Soy Crumbles	½ cup	9
Soy Protein Isolate Powder, Plain	⅓ cup	53
Textured Soy Protein, Dry	¼ cup	33
Tempeh	½ cup	53
Tofu	½ cup	25

Source: United States Department of Agriculture Nutrient Database.

Sub-analysis of the data revealed three interesting findings. First, baseline hot flash frequency did not impact efficacy. That is, the percent reduction in hot flash frequency was similar regardless of whether women had two hot flashes per day at baseline or 10 hot flashes per day. Second, hot flashes were reduced more in studies >12 weeks in duration versus shorter-term studies. This finding indicates the effects of isoflavones are not transient. Third, and most important, supplements that provided higher amounts of genistein were considerably more efficacious than supplements low in this isoflavone. This finding is important because the two primary types of supplements that are commercially available and that have been used in the clinical trials have markedly different isoflavone profiles. One is high in genistein and daidzein but low in glycitein, which is similar to the isoflavone profile of soyfoods, whereas the other one is very low in genistein and high in daidzein and glycitein.

In studies that intervened with supplements providing ≥18.8 mg genistein (the median for all studies), hot flash frequency was reduced by almost 27% beyond the placebo effect whereas in trials providing less than this amount, frequency was reduced by only about 12.5% (difference between groups, P = 0.03). The greater reduction in response to genistein-rich supplements is consistent with several lines of evidence indicating that genistein is more potent than the other two soybean isoflavones.[33,34]

Collectively, the data make a convincing case that isoflavones can be of help to women who experience hot flashes. Several trials published subsequent to the 2012 meta-analysis are supportive of efficacy.[35-37] The one notable unsupportive trial employed an experimental design inconsistent with guidelines for conducting trials evaluating hot flashes.[38]

The level of relief provided by isoflavones is consistent with the degree of benefit deemed satisfactory by women seeking non-hormonal treatments for hot flashes.[39] The amount of isoflavones (~50 mg) providing symptom relief is found in approximately two 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.[40] Estrogen therapy reduces postmenopausal bone loss and hip fracture risk by approximately one-third.[41] Data shows that the protective effects against hip fracture are lost within two years of cessation of estrogen therapy.[42] 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.[43]

Two prospective Asian 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 category were compared to women in the lowest. This degree of protection is similar to that noted for estrogen therapy.[41] In one of the studies, approximately 1,800 fractures of all types occurred in the 24,000 postmenopausal Shanghai women who were followed for 4.5 years.[44] In the other study, there were almost 700 hip fractures (the only site studied) among the 35,000 postmenopausal Singaporean women during the 7-year follow up period.[45]

In a third prospective epidemiologic study, which involved U.S. Seventh-day Adventists, soymilk intake was significantly inversely related to risk of osteoporosis.[46] However, evidence suggests the beneficial effect of soymilk was due to its calcium content rather than its isoflavone content since dairy product intake was similarly protective. Although the results of this study[46] and the two previously discussed Asian studies[44,45] are intriguing, definitive conclusions about the skeletal effects of soyfoods can only be based on the results from appropriately designed clinical studies.

Danish researchers recently meta-analyzed the results of 26 randomized controlled trials involving 2,652 peri- or postmenopausal women that evaluated the effect of isoflavone exposure on bone mineral density (BMD).[47] They found that at both the lumbar spine and the femoral neck, in comparison to the control/placebo, isoflavone treatment was associated with a significantly higher weighted mean difference of BMD change. However, when sub-analyzing the data, the benefit of treatment was enhanced when limiting the analysis to trials intervening with isoflavones in aglycone form, whereas the benefit disappeared when only studies with formulations comprising predominantly isoflavone glycosides were included.

Of the many intervention trials, four stand out for their size and duration (≥2 years duration). Two were conducted in the U.S.,[38,48] one in Italy[49] and one in Taiwan.[50] Three of the four trials failed to show favorable effects on BMD. The one trial that did, found that in osteopenic Italian women consuming 54 mg/d genistein, BMD at the spine and hip increased markedly over a three-year period whereas in the placebo group there were marked decreases.[49] This trial intervened with genistein in aglycone form.

The failure of three of the four large trials to show skeletal benefits of isoflavones certainly casts doubt upon the efficacy of isoflavones. That being said, research from Purdue University using novel methodology highlights the potential skeletal benefits of isoflavones and possibly provides at least a partial explanation for the lack of effect in the longer-term clinical trials.[51] For this cross-over study, 24 healthy postmenopausal women were administered daily either different isoflavone supplements or risedronate, a bisphosphonate anti-osteoporotic drug, for 50 days.[51] Prior to the intervention, each woman was injected with 41Ca, a rare isotope of calcium that has an exceptionally long half-life, which makes it possible to precisely detect changes in bone calcium content. Risedronate increased bone calcium content by a statistically significant 15.3 percent. Hence, the methodology employed in this study identified the bone-protective effects of this drug. Risedronate is known to reduce risk of developing both vertebral and hip fractures by approximately 50 percent.[52]

In response to a daily supplement containing 105 mg isoflavones, bone calcium content significantly increased by 7.6 percent. Thus, at this dose level, isoflavones were about half as potent as a well-established drug used to treat osteoporosis. The authors of this study concluded that "…the use of soy isoflavones presents minimal to negligible risk to postmenopausal women… and can be used long term for some protection against postmenopausal bone loss." This trial also showed that isoflavone doses much higher than the 105 mg dose, were actually much less efficacious. Two of the three previously cited clinical trials used very large doses, which might explain why they failed to show isoflavones affect BMD.[38,50]

Regardless of the effects of isoflavones, soyfoods may benefit bone because they provide high-quality protein,[53] which may promote bone health.[54-56] In addition, some soyfoods are good sources of calcium as well as vitamin D.[57] Importantly, the absorption of calcium from calcium-set tofu[58] and calcium-fortified soymilk[57,59] is comparable to the absorption of this mineral from cow's milk. Therefore, for several reasons, soyfoods can contribute to a bone-healthful diet.

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

Heart Health

Soyfoods potentially offer protection against heart disease through several mechanisms. For example, soyfoods are low in saturated fat and high in polyunsaturated fat.[60] When soyfoods replace common sources of protein in the U.S. diet, as a result of the favorable change in fatty acid intake, estimates are that circulating LDL-cholesterol concentrations may be reduced by as much as 4 percent.[61] There is also evidence indicating that when unsaturated fat replaces saturated fat, endothelial function[62] and cholesterol efflux capacity[63] will be enhanced.

Independent of fat content, soy protein directly lowers blood cholesterol levels, an attribute that was formally recognized by the U.S. Food and Drug Administration (FDA) in 1999.[64] Although the FDA is currently reevaluating evidence in support of the claim, meta-analyses of the clinical data show soy protein lowers LDL-cholesterol approximately 4 percent.[61,65-73] Soy protein may also modestly lower blood pressure.[71,74-76]

Finally, there is evidence that isoflavones improve endothelial function in postmenopausal women.[52,53] For a more extensive discussion on heart health, see the Soy Connection *Soy & Heart Health* fact sheet.

> Soyfoods may offer protection against heart disease, as they are low in saturated fat and high in polysaturated fats.

Breast Cancer

The role of soyfoods in reducing breast cancer risk has been rigorously investigated for more than two decades. A meta-analysis of epidemiologic studies published in 2013 that included 12 studies from Asia found that higher soy intake was associated with a statistically significant 29 percent reduction in the risk of developing breast cancer.[3] However, there is intriguing evidence indicating that to derive this benefit, soy consumption must occur during childhood and/or adolescence.[77-79]

Despite the results of the epidemiologic research noted above[3] and the low breast cancer mortality rates in Japan,[80] the relationship between soyfoods and breast cancer has been controversial. This controversy is due to concern, based almost exclusively on in vitro and rodent data, that isoflavones may be contraindicated for women with breast cancer and women at high risk of developing this disease.[81] However, as discussed, the clinical and epidemiologic data show that soyfoods are safe for women with breast cancer and may even benefit them.

Although no clinical trials evaluating the effects of soy or isoflavones on breast cancer recurrence have been conducted, many studies have shown that isoflavone exposure does not adversely affect markers of breast cancer risk including mammographic density[82,83] and in vivo breast cell proliferation.[84-89] Furthermore, prospective epidemiologic data show that post-diagnosis soy intake improves prognosis. Results of a meta-analysis of five prospective studies are in support of this statement, two from the U.S. and three from China, involving more than 11,000 women with breast cancer, which found post-diagnosis soy intake was associated with reductions in both breast cancer recurrence (hazard ratio, 0.84; 95% confidence interval: 0.71, 0.99) and mortality (hazard ratio, 0.74; 95% confidence interval: 0.64, 0.85). Importantly, soy consumption was similarly beneficial in Asian and non-Asian women. In contrast to studies in mice, the epidemiologic data suggest that soy consumption may enhance the efficacy of chemotherapeutic agents used to treat breast cancer.[90,91]

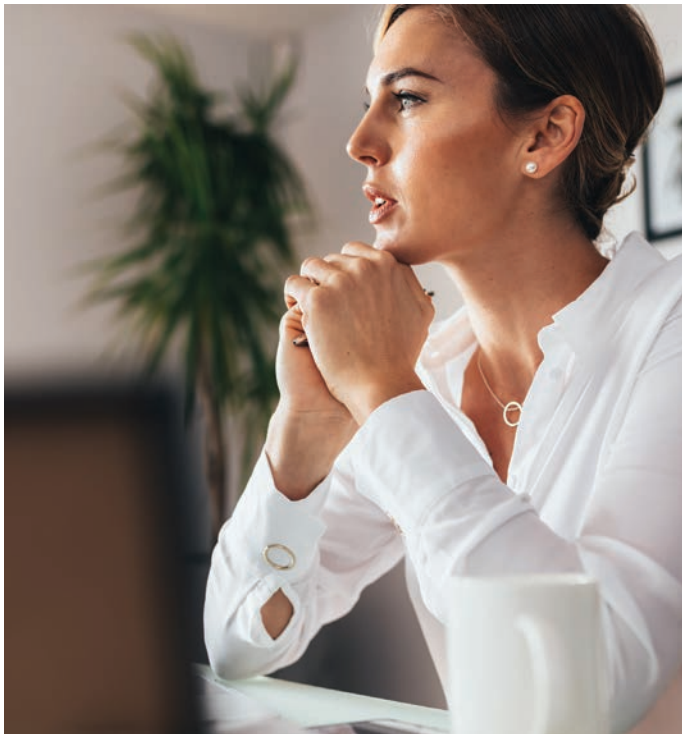
Given the previous data, it is not surprising that after a multi-year comprehensive review of the relevant literature, the European Food Safety Authority concluded that isoflavone supplements do not increase breast cancer risk when taken by postmenopausal women.[92] In 2012, the American Cancer Society[93] and the American Institute for Cancer Research (AICR)[94] concluded that soyfoods can be safely consumed by breast cancer patients. In 2018, a combined report from the AICR and the World Cancer Research Fund concluded there is a possible link between consuming soyfoods and improved survival from breast cancer.[95]

> The American Cancer Society and the American Institute for Cancert Research concluded that soyfoods can be safely consumed by breast cancer patients.

In many respects, scientific perspective has transformed from concern regarding women with breast cancer consuming soyfoods to recognition of the potential benefits. For more a extensive discussion on heart health, see the Soy Connection *Soy & the Breast Cancer Patient* fact sheet.

Skin Health

Interest in the effects of soy on overall skin health is not surprising given that isoflavones bind to ERs, which are present in the skin,[96,97] and that estrogen therapy is thought to improve a number of skin parameters[98-101] including skin elasticity,[102] water-holding capacity,[103] pigmentation,[104] and vascularity.[105] Skin appendages, such as hair follicles, are also influenced by estrogens.[106]



Several trials suggest that isoflavones help to reduce wrinkles. For example, in one study, two groups of 20 healthy postmenopausal women aged 50 to 65 years were instructed to consume their usual diet with or without 20 g/d of an isoflavone-rich soy protein for three months.[107] There were statistically significant improvements in facial-skin wrinkling, discoloration and overall appearance in the supplement group. In another study involving 26 Japanese women in their late 30s and 40s, over a three-month period, use of supplements that provided 40 mg/d isoflavones led to a statistically significant decrease in fine wrinkles, whereas no change occurred in the placebo group.[108]

A 14-week trial conducted by Jenkins et al.[109] involving 159 postmenopausal women found that a beverage containing isoflavones statistically significantly reduced wrinkles by on average 10 percent. There was also a positive correlation between baseline wrinkle depth and the response to the isoflavone-containing beverage; that is, the greater the wrinkle depth at baseline, the greater the improvement. In addition to the effect on wrinkles, there was also a statistically significant increase in collagen synthesis.

Finally, Japanese researchers recently examined the effect of soymilk consumption on subjective and objective measures of skin health in 60 women.[110] In this 8-week study, when compared to baseline, soymilk improved skin condition as subjectively assessed from scores of overall satisfaction, dryness, moisture, elasticity, coarseness and pigmentation. In addition, skin biopsies showed significant improvement in the stratum corneum morphology.

Endometrial Tissue

Endometrial cancer, cancer of the corpus uteri, represents the most common gynecological malignancy in the industrialized world and is the seventh most common cancer among females. Although, incidence and mortality rates vary markedly among geographical regions and countries.[80] The highest rates are in the U.S. and Europe and the lowest in Asia and Africa.[111] There is concern that because of the presence of isoflavones, soyfoods could increase risk of developing endometrial cancer and stimulate the growth of existing endometrial tumors. Ever users of unopposed estrogen therapy are about two to three times more likely to develop endometrial cancer as never users.[112-114]

After reviewing 25 clinical studies that measured endometrial thickness and nine that measured histopathological changes, the European Food

Safety Authority concluded that isoflavones do not adversely affect the endometrium.[115] Interestingly, a recently published meta-analysis of the clinical data found that when all studies (N=23; 2,167 participants) were included in the analysis there was no effect of isoflavones on endometrial thickness; however, there was a significant (P=0.04) decrease in thickness when considering only the seven North American trials which involved 726 women.[116] In contrast, there was small increase in thickness among women involved in the three Asian trials but none of these studies actually intervened with soybean-derived isoflavones.

A recent meta-analysis of 10 observational studies, eight case-control and two prospective, found soy intake was inversely associated with endometrial cancer risk with an overall risk estimate (RE) of 0.81 (95% confidence interval: 0.72, 0.91).[117] Subgroup analyses found statistically significant protective effects for both Asian (RE: 0.79, 95% CI: 0.66, 0.95) and non-Asian (RE: 0.83, 95% CI: 0.71, 0.96) populations. Finally, Bitto et al.[118] found that in a group of premenopausal women with non-atypical endometrial hyperplasia, genistein (54 mg/d) improved symptoms after six months to approximately the same degree as norethisterone. Hence, the authors concluded that genistein might be useful for the management of endometrial hyperplasia without atypia in women that cannot be treated with progestin.[118]

Fertility

There are a number of issues involving soyfoods that have given rise to quite lively discussions in the peer-reviewed literature. One of these somewhat ironically, given the large populations of Asian countries that have historically consumed soy, is the impact of soy on fertility. In women, soyfoods appear to increase the length of the menstrual cycle although ovulation is not prevented it is simply delayed by one day.[119] According to limited epidemiologic data, this minor effect on menstrual cycle length could help to decrease breast cancer risk.[120]

There is some evidence that isoflavones aid fertility. A prospective study found that among 315 women who collectively underwent 520 assisted reproductive technology cycles soy isoflavone intake was positively related to live birth rates.[121] Similarly, among women undergoing in vitro fertilization, soy consumption appeared to negate the adverse reproductive effects of the endocrine disruptor bisphenol A (BPA).[122] Although the low isoflavone intake among the soy-consumers (mean intake, 3.4 mg/d) in this study raise doubt about the plausibility of these findings, they do agree with animal data.[123,124]

Summary and Conclusions

Soyfoods are uniquely-rich dietary sources of isoflavones, compounds classified as phytoestrogens but that differ from the hormone estrogen. Epidemiologic and clinical data suggest that soyfoods can make important contributions to the health of women, particularly postmenopausal women. Soyfoods potentially reduce CHD through multiple mechanisms. Clinical research indicates that isoflavones alleviate hot flashes although the evidence that they reduce bone loss is mixed. Irrespective of the skeletal effects of isoflavones, soyfoods can be part of a bone-healthy diet as they provide high-quality protein and many are good sources of well-absorbed calcium.

Adult soy intake does not appear to reduce breast cancer risk although evidence suggests that soy consumption during childhood and adolescence does. Claims that soyfoods are contraindicated for breast cancer patients are unsupported by the clinical and epidemiologic evidence; the former shows neither soy nor isoflavones adversely affect markers of breast cancer risk and the latter show that post-diagnosis soy intake reduces breast cancer recurrence and mortality. Soy consumption may decrease risk of developing endometrial cancer and preliminary clinical research indicates that isoflavones may improve skin health. Finally, soyfood consumption does not adversely affect reproduction in women.

References

1. Messina M, Lane B. Soy protein, soybean isoflavones, and coronary heart disease risk: Where do we stand? Future Lipidology. 2007;255-74.

2. Ma DF, Qin LQ, Wang PY, et al. Soy isoflavone intake increases bone mineral density in the spine of menopausal women: meta-analysis of randomized controlled trials. Clin Nutr. 2008;27(1):57-64.

3. Wu AH, Yu MC, Tseng CC, et al. Epidemiology of soy exposures and breast cancer risk. Br J Cancer. 2008;98(1):9-14.

4. Howes LG, Howes JB, Knight DC. Isoflavone therapy for menopausal flushes: a systematic review and meta-analysis. Maturitas. 2006;55(3):203-11.

5. Gollschewski S, Kitto S, Anderson D, et al. Women's perceptions and beliefs about the use of complementary and alternative medicines during menopause. Complement Thr Med. 2008;16(3):163-8.

6. Helferich WG, Andrade JE, Hoagland MS. Phytoestrogens and breast cancer: a complex story. Inflammopharmacology. 2008;16(5):219-26.

7. Franke AA, Custer LJ, Wang W, et al. HPLC analysis of isoflavonoids and other phenolic agents from foods and from human fluids. Proc Soc Exp Biol Med. 1998;217(3):263-73.

8. Messina M, Nagata C, Wu AH. Estimated Asian adult soy protein and isoflavone intakes. Nutr Cancer. 2006;55(1):1-12.

9. Horn-Ross PL, John EM, Canchola AJ, et al. Phytoestrogen intake and endometrial cancer risk. J Natl Cancer Inst. 2003;95(15):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;131(4):1202-6.

11. de Kleijn MJ, van der Schouw YT, Wilson PW, et al. Intake of dietary phytoestrogens is low in postmenopausal women in the United States: the Framingham study (1-4). J Nutr. 2001;131(6):1826-32.

12. van Erp-Baart MA, Brants HA, Kiely M, et al. Isoflavone intake in four different European countries: the VENUS approach. Br J Nutr. 2003;89 Suppl 1S25-30.

13. van der Schouw YT, Kreijkamp-Kaspers S, Peeters PH, et al. Prospective study on usual dietary phytoestrogen intake and cardiovascular disease risk in Western women. Circulation. 2005;111(4):465-71.

14. Boker LK, Van der Schouw YT, De Kleijn MJ, et al. Intake of dietary phytoestrogens by Dutch women. J Nutr. 2002;132(6):1319-28.

15. Faulkner-Hogg KB, Selby WS, Loblay RH. Dietary analysis in symptomatic patients with coeliac disease on a gluten-free diet: the role of trace amounts of gluten and non-gluten food intolerances. Scand J Gastroenterol. 1999;34(8):784-9.

16. Murphy PA, Barua K, Hauck CC. Solvent extraction selection in the determination of isoflavones in soy foods. Journal of chromatography B, Analytical technologies in the biomedical and life sciences. 2002;777(1-2):129-38.

17. Rowland I, Faughnan M, Hoey L, et al. Bioavailability of phyto-oestrogens. Br J Nutr. 2003;89 Suppl 1S45-58.

18. Kuiper GG, Carlsson B, Grandien K, et al. Comparison of the ligand binding specificity and transcript tissue distribution of estrogen receptors alpha and beta. Endocrinology. 1997;138(3):863-70.

19. Kuiper GG, Lemmen JG, Carlsson B, et al. Interaction of estrogenic chemicals and phytoestrogens with estrogen receptor beta. Endocrinology. 1998;139(10):4252-63.

20. An J, Tzagarakis-Foster C, Scharschmidt TC, et al. Estrogen Receptor beta -Selective Transcriptional Activity and Recruitment of Coregulators by Phytoestrogens. J Biol Chem. 2001;276(21):17808-14.

21. Margeat E, Bourdoncle A, Margueron R, et al. Ligands Differentially Modulate the Protein Interactions of the Human Estrogen Receptors alpha and beta. J Mol Biol. 2003;326(1):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;51(26):7632-5.

23. Pike AC, Brzozowski AM, Hubbard RE, et al. Structure of the ligand-binding domain of oestrogen receptor beta in the presence of a partial agonist and a full antagonist. EMBO J. 1999;18(17):4608-18.

24. Lindberg MK, Moverare S, Skrtic S, et al. Estrogen receptor (ER)-beta reduces ERalpha-regulated gene transcription, supporting a "ying yang" relationship between ERalpha and ERbeta in mice. Mol Endocrinol. 2003;17(2):203-8.

25. Maehle BO, Collett K, Tretli S, et al. Estrogen receptor beta--an independent prognostic marker in estrogen receptor alpha and progesterone receptor-positive breast cancer? APMIS. 2009;117(9):644-50.

26. Sareddy GR, Vadlamudi RK. Cancer therapy using natural ligands that target estrogen receptor beta. Chin J Nat Med. 2015;13(11):801-7.

27. Brzezinski A, Adlercreutz H, Shaoul R, et al. Short-term effect of phytoestrogen-rich diet on postmenopausal women. Menopause. 1997;489-94.

28. Diel P, Geis RB, Caldarelli A, et al. 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;221(1-2):21-32.

29. Yildiz MF, Kumru S, Godekmerdan A, et al. Effects of raloxifene, hormone therapy, and soy isoflavone on serum high-sensitive C-reactive protein in postmenopausal women. Int JGynaecol Obstet. 2005;90(2):128-33.

30. Kronenberg F. Hot flashes: epidemiology and physiology. Ann N Y Acad Sci. 1990;59252-86; discussion 123-33.

31. Adlercreutz H, Hamalainen E, Gorbach S, et al. Dietary phyto-oestrogens and the menopause in Japan. Lancet. 1992;339(8803):1233.

32. Taku K, Melby MK, Kronenberg F, et al. Extracted or synthesized soybean isoflavones reduce menopausal hot flash frequency and severity: systematic review and meta-analysis of randomized controlled trials. Menopause. 2012;19(7):776-90.

33. Weaver CM, Martin BR, Jackson GS, et al. Antiresorptive effects of phytoestrogen supplements compared with estradiol or risedronate in postmenopausal women using (41)Ca methodology. J Clin Endocrinol Metab. 2009;94(10):3798-805.

34. Muthyala RS, Ju YH, Sheng S, et al. Equol, a natural estrogenic metabolite from soy isoflavones: convenient preparation and resolution of R- and S-equols and their differing binding and biological activity through estrogen receptors alpha and beta. Bioorg Med Chem. 2004;12(6):1559-67.

35. Imhof M, Gocan A, Schmidt M. Soy germ extract alleviates menopausal hot flushes: placebo-controlled double-blind trial. Eur J Clin Nutr. 2018.

36. Chi X-X, Zhang T. The effects of soy isoflavone on bone density in north region of climacteric Chinese women. Journal of clinical biochemistry and nutrition. 2013;53(2):102-7.

37. Bitto A, Arcoraci V, Alibrandi A, et al. Visfatin correlates with hot flashes in postmenopausal women with metabolic syndrome: effects of genistein. Endocrine. 2017;55(3):899-906.

38. Levis S, Strickman-Stein N, Ganjei-Azar P, et al. Soy isoflavones in the prevention of menopausal bone loss and menopausal symptoms: A randomized, double-blind trial. Arch Intern Med. 2011;171(15):1363-9.

39. Butt DA, Deng LY, Lewis JE, et al. Minimal decrease in hot flashes desired by postmenopausal women in family practice. Menopause. 2007;14(2):203-7.

40. Finkelstein JS, Brockwell SE, Mehta V, et al. Bone mineral density changes during the menopause transition in a multiethnic cohort of women. J Clin Endocrinol Metab. 2008;93(3):861-8.

41. 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;288(3):321-33.

42. LaCroix AZ, Chlebowski RT, Manson JE, et al. Health outcomes after stopping conjugated equine estrogens among postmenopausal women with prior hysterectomy: a randomized controlled trial. JAMA. 2011;305(13):1305-14.

43. Brandi ML, Gennari C. Ipriflavone: new insights into its mechanisms of action on bone remodeling. Calcif Tissue Int. 1993;52(2):151-2.

44. Zhang X, Shu XO, Li H, et al. Prospective cohort study of soy food consumption and risk of bone fracture among postmenopausal women. Arch Intern Med. 2005;165(16):1890-5.

45. Koh WP, Wu AH, Wang R, et al. Gender-specific associations between soy and risk of hip fracture in the Singapore Chinese Health Study. Am J Epidemiol. 2009;170(7):901-9.

46. Matthews VL, Knutsen SF, Beeson WL, et al. Soy milk and dairy consumption is independently associated with ultrasound attenuation of the heel bone among postmenopausal women: the Adventist Health Study-2. Nutr Res. 2011;31(10):766-75.

47. Lambert MNT, Hu LM, Jeppesen PB. A systematic review and meta-analysis of the effects of isoflavone formulations against estrogen-deficient bone resorption in peri- and postmenopausal women. Am J Clin Nutr. 2017;106(3):801-11.

48. Alekel DL, Van Loan MD, Koehler KJ, et al. The soy isoflavones for reducing bone loss (SIRBL) study: a 3-y randomized controlled trial in postmenopausal women. Am J Clin Nutr. 2010;91(1):218-30.

49. Marini H, Bitto A, Altavilla D, et al. Breast safety and efficacy of genistein aglycone for postmenopausal bone loss: a follow-up study. J Clin Endocrinol Metab. 2008;93(12):4787-96.

50. Tai TY, Tsai KS, Tu ST, et al. The effect of soy isoflavone on bone mineral density in postmenopausal Taiwanese women with bone loss: a 2-year randomized double-blind placebo-controlled study. Osteoporos Int. 2012;23(5):1571-80.

51. Pawlowski JW, Martin BR, McCabe GP, et al. Impact of equol-producing capacity and soy-isoflavone profiles of supplements on bone calcium retention in postmenopausal women: a randomized crossover trial. Am J Clin Nutr. 2015;102(3):695-703.

52. Adachi JD, Rizzoli R, Boonen S, et al. Vertebral fracture risk reduction with risedronate in post-menopausal women with osteoporosis: a meta-analysis of individual patient data. Aging clinical and experimental research. 2005;17(2):150-6.

53. Rand WM, Pellett PL, Young VR. Meta-analysis of nitrogen balance studies for estimating protein requirements in healthy adults. Am J Clin Nutr. 2003;77(1):109-27.

54. Darling AL, Millward DJ, Torgerson DJ, et al. Dietary protein and bone health: a systematic review and meta-analysis. Am J Clin Nutr. 2009;90(6):1674-92.

55. Jesudason D, Clifton P. The interaction between dietary protein and bone health. J Bone Miner Metab. 2011;29(1):1-14.

56. Shams-White MM, Chung M, Du M, et al. Dietary protein and bone health: a systematic review and meta-analysis from the National Osteoporosis Foundation. Am J Clin Nutr. 2017.

57. 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;135(10):2379-82.

58. Weaver CM, Heaney RP, Connor L, et al. Bioavailability of calcium from tofu vs. milk in premenopausal women. J Food Sci. 2002;683144-7.

59. Tang AL, Walker KZ, Wilcox G, et al. Calcium absorption in Australian osteopenic post-menopausal women: an acute comparative study of fortified soymilk to cows' milk. Asia Pacific journal of clinical nutrition. 2010;19(2):243-9.

60. Slavin M, Kenworthy W, Yu LL. Antioxidant properties, phytochemical composition, and antiproliferative activity of Maryland-grown soybeans with colored seed coats. J Agric Food Chem. 2009;57(23):11174-85.

61. Jenkins DJ, Mirrahimi A, Srichaikul K, et al. Soy protein reduces serum cholesterol by both intrinsic and food displacement mechanisms. J Nutr. 2010;140(12):2302S-11S.

62. Weech M, Altowaijri H, Mayneris-Perxachs J, et al. Replacement of dietary saturated fat with unsaturated fats increases numbers of circulating endothelial progenitor cells and decreases numbers of microparticles: findings from the randomized, controlled Dietary Intervention and VAScular function (DIVAS) study. Am J Clin Nutr. 2018.

63. Liu X, Garban J, Jones PJ, et al. Diets low in saturated fat with different unsaturated fatty acid profiles similarly increase serum-mediated cholesterol efflux from thp-1 macrophages in a population with or at risk for metabolic syndrome: the canola oil multicenter intervention trial J Nutr. 2018;148721-8.

64. Food labeling: health claims; soy protein and coronary heart disease. Food and Drug Administration, HHS. Final rule. Fed Regist. 1999;64(206):57700-33.

65. Zhan S, Ho SC. Meta-analysis of the effects of soy protein containing isoflavones on the lipid profile. Am J Clin Nutr. 2005;81(2):397-408.

66. Harland JI, Haffner TA. Systematic review, meta-analysis and regression of randomised controlled trials reporting an association between an intake of circa 25 g soya protein per day and blood cholesterol. Atherosclerosis. 2008;200(1):13-27.

67. Anderson JW, Bush HM. Soy protein effects on serum lipoproteins: A quality assessment and meta-analysis of randomized, controlled studies. J Am Coll Nutr. 2011;30(2):79-91.

68. Benkhedda K, Boudrault C, Sinclair SE, et al. Food Risk Analysis Communication. Issued By Health Canada's Food Directorate. Health Canada's Proposal to Accept a Health Claim about Soy Products and Cholesterol Lowering. Int Food Risk Anal J. 2014;4:22 | doi: 10.5772/59411.

69. Tokede OA, Onabanjo TA, Yansane A, et al. Soya products and serum lipids: a meta-analysis of randomised controlled trials. Br J Nutr. 2015;114(6):831-43.

70. Yang B, Chen Y, Xu T, et al. Systematic review and meta-analysis of soy products consumption in patients with type 2 diabetes mellitus. Asia Pacific journal of clinical nutrition. 2011;20(4):593-602.

71. Hooper L, Kroon PA, Rimm EB, et al. Flavonoids, flavonoid-rich foods, and cardiovascular risk: a meta-analysis of randomized controlled trials. Am J Clin Nutr. 2008;88(1):38-50.

72. Reynolds K, Chin A, Lees KA, et al. A meta-analysis of the effect of soy protein supplementation on serum lipids. Am J Cardiol. 2006;98(5):633-40.

73. Weggemans RM, Trautwein EA. Relation between soy-associated isoflavones and LDL and HDL cholesterol concentrations in humans: a meta-analysis. Eur J Clin Nutr. 2003;57(8):940-6.

74. Dong JY, Tong X, Wu ZW, et al. Effect of soya protein on blood pressure: a meta-analysis of randomised controlled trials. Br J Nutr. 2011;106(3):317-26.

75. Taku K, Lin N, Cai D, et al. Effects of soy isoflavone extract supplements on blood pressure in adult humans: systematic review and meta-analysis of randomized placebo-controlled trials. J Hypertens. 2010;28(10):1971-82.

76. Liu XX, Li SH, Chen JZ, et al. Effect of soy isoflavones on blood pressure: A meta-analysis of randomized controlled trials. Nutrition, metabolism, and cardiovascular diseases : NMCD. 2012;22(6):463-70.

77. 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;211-9.

78. Shu XO, Jin F, Dai Q, et al. Soyfood intake during adolescence and subsequent risk of breast cancer among Chinese women. Cancer Epidemiol Biomarkers Prev. 2001;10(5):483-8.

79. Wu AH, Yu MC, Tseng CC, et al. Dietary patterns and breast cancer risk in Asian American women. Am J Clin Nutr. 2009;89(4):1145-54.

80. Pisani P, Bray F, Parkin DM. Estimates of the world-wide prevalence of cancer for 25 sites in the adult population. Int J Cancer. 2002;97(1):72-81.

81. Messina M, McCaskill-Stevens W, Lampe JW. Addressing the soy and breast cancer relationship: review, commentary, and workshop proceedings. J Natl Cancer Inst. 2006;98(18):1275-84.

82. Hooper L, Madhavan G, Tice JA, et al. Effects of isoflavones on breast density in pre- and post-menopausal women: a systematic review and meta-analysis of randomized controlled trials. Hum Reprod Update. 2010;16(6):745-60.

83. Wu AH, Spicer D, Garcia A, et al. Double-blind randomized 12-month soy intervention had no effects on breast MRI fibroglandular tissue density or mammographic density. Cancer Prev Res (Phila). 2015;8(10):942-51.

84. Hargreaves DF, Potten CS, Harding C, et al. Two-week dietary soy supplementation has an estrogenic effect on normal premenopausal breast. J Clin Endocrinol Metab. 1999;84(11):4017-24.

85. Sartippour MR, Rao JY, Apple S, et al. A pilot clinical study of short-term isoflavone supplements in breast cancer patients. Nutr Cancer. 2004;49(1):59-65.

86. Palomares MR, Hopper L, Goldstein L, et al. Effect of soy isoflavones on breast proliferation in postmenopausal breast cancer survivors. Breast Cancer Res Treatment. 2004;88 (Suppl 1)4002 (Abstract).

87. Cheng G, Wilczek B, Warner M, et al. Isoflavone treatment for acute menopausal symptoms. Menopause. 2007;14(3 Pt 1):468-73.

88. Khan SA, Chatterton RT, Michel N, et al. Soy isoflavone supplementation for breast cancer risk reduction: A randomized phase II trial. Cancer Prev Res (Phila). 2012;5(2):309-19.

89. Shike M, Doane AS, Russo L, et al. The effects of soy supplementation on gene expression in breast cancer: a randomized placebo-controlled study. J Natl Cancer Inst. 2014;106(9).

90. Kang X, Zhang Q, Wang S, et al. Effect of soy isoflavones on breast cancer recurrence and death for patients receiving adjuvant endocrine therapy. CMAJ. 2010;182(17): 1857-62.

91. Nechuta SJ, Caan BJ, Chen WY, et al. Soy food intake after diagnosis of breast cancer and survival: an in-depth analysis of combined evidence from cohort studies of US and Chinese women. Am J Clin Nutr. 2012;96(1):123-32.

92. EFSA ANS Panel (EFSA Panel on Food Additives and Nutrient Sources added to Food), 2015. Scientific opinion on the risk assessment for peri- and post-menopausal women taking food supplements containing isolated isoflavones. EFSA J. 2015;13(10):4246 (342 pp).

93. Rock CL, Doyle C, Demark-Wahnefried W, et al. Nutrition and physical activity guidelines for cancer survivors. CA Cancer J Clin. 2012;62(4):242-74.

94. American Institute for Cancer Research. Soy is safe for breast cancer survivors. http://wwwaicrorg/cancer-research-update/november_21_2012/cru-soy-safehtml (accessed Feburary 5, 2013). 2012.

95. American Institute for Cancer Research, World Cancer Research Fund. Diet, nutrition, physical activity and breast cancer survivors. Updated 2018. Continuous update project (http://www.aicr.org/continuous-update-project/breast-cancer.html). Accessed July 14, 2018.

96. Thornton MJ, Taylor AH, Mulligan K, et al. The distribution of estrogen receptor beta is distinct to that of estrogen receptor alpha and the androgen receptor in human skin and the pilosebaceous unit. J Investig Dermatol Symp Proc. 2003;8(1):100-3.

97. Thornton MJ, Taylor AH, Mulligan K, et al. Oestrogen receptor beta is the predominant oestrogen receptor in human scalp skin. Exp Dermatol. 2003;12(2):181-90.

98. Hall G, Phillips TJ. Estrogen and skin: the effects of estrogen, menopause, and hormone replacement therapy on the skin. J Am Acad Dermatol. 2005;53(4):555-68; quiz 69-72.

99. Hall GK, Phillips TJ. Skin and hormone therapy. Clin Obstet Gynecol. 2004;47(2):437-49.

100. Schmidt JB, Binder M, Macheiner W, et al. Treatment of skin ageing symptoms in perimenopausal females with estrogen compounds. A pilot study. Maturitas. 1994;20(1):25-30.

101. Sator PG, Schmidt JB, Rabe T, et al. Skin aging and sex hormones in women -- clinical perspectives for intervention by hormone replacement therapy. Exp Dermatol. 2004;13 Suppl 436-40.

102. Pierard GE, Letawe C, Dowlati A, et al. Effect of hormone replacement therapy for menopause on the mechanical properties of skin. J Am Geriatr Soc. 1995;43(6):662-5.

103. Pierard-Franchimont C, Letawe C, Goffin V, et al. Skin water-holding capacity and transdermal estrogen therapy for menopause: a pilot study. Maturitas. 1995;22(2):151-4.

104. Snell RS, Turner R. Skin pigmentation in relation to the menstrual cycle. J Invest Dermatol. 1966;47(2):147-55.

105. Harvell J, Hussona-Saeed I, Maibach HI. Changes in transepidermal water loss and cutaneous blood flow during the menstrual cycle. Contact Dermatitis. 1992;27(5): 294-301.

106. Thornton MJ. Oestrogen functions in skin and skin appendages. Expert Opin Ther Targets. 2005;9(3):617-29.

107. Draelos ZD, Blair R, Tabor A. Oral soy supplementation and dermatology. Cosmetic Dermatology. 2007;20202-4.

108. Izumi T, Makoto S, Obata A, et al. Oral intake of soy isoflavone aglycone improves the aged skin of adult women. J Nutr Sci Vitaminol. 2007;53(1):57-62.

109. Jenkins G, Wainwright LJ, Holland R, et al. Wrinkle reduction in post-menopausal women consuming a novel oral supplement: a double-blind placebo-controlled randomised study. International journal of cosmetic science. 2013;3622-31.

110. Nagino T, Kaga C, Kano M, et al. Effects of fermented soymilk with Lactobacillus casei Shirota on skin condition and the gut microbiota: a randomised clinical pilot trial. Beneficial microbes. 2018;9(2):209-18.

111. Parkin DM, Pisani P, Ferlay J. Estimates of the worldwide incidence of 25 major cancers in 1990. Int J Cancer. 1999;80(6):827-41.

112. Weiderpass E, Adami HO, Baron JA, et al. Risk of endometrial cancer following estrogen replacement with and without progestins. J Natl Cancer Inst. 1999;91(13):1131-7.

113. Role of progestogen in hormone therapy for postmenopausal women: position statement of The North American Menopause Society. Menopause. 2003;10(2):113-32.

114. Grady D, Gebretsadik T, Kerlikowske K, et al. Hormone replacement therapy and endometrial cancer risk: a meta-analysis. Obstet Gynecol. 1995;85(2):304-13.

115. EFSA ANS Panel (EFSA Panel on Food Additives and Nutrient Sources added to Food), 2015. Scientific opinion on the risk assessment for peri- and post-menopausal women taking food supplements containing isolated isoflavones. EFSA J.13(10):4246 (342 pp).

116. Liu J, Yuan F, Gao J, et al. Oral isoflavone supplementation on endometrial thickness: a meta-analysis of randomized placebo-controlled trials. Oncotarget. 2016;7(14):17369-79.

117. Zhang GQ, Chen JL, Liu Q, et al. Soy intake is associated with lower endometrial cancer risk: A systematic review and meta-analysis of observational studies. Medicine (Baltimore). 2015;94(50):e2281.

118. Bitto A, Granese R, Triolo O, et al. Genistein aglycone: a new therapeutic approach to reduce endometrial hyperplasia. Phytomedicine. 2010;17(11):844-50.

119. Hooper L, Ryder JJ, Kurzer MS, et al. Effects of soy protein and isoflavones on circulating hormone concentrations in pre- and post-menopausal women: a systematic review and meta-analysis. Hum Reprod Update. 2009;15(4):423-40.

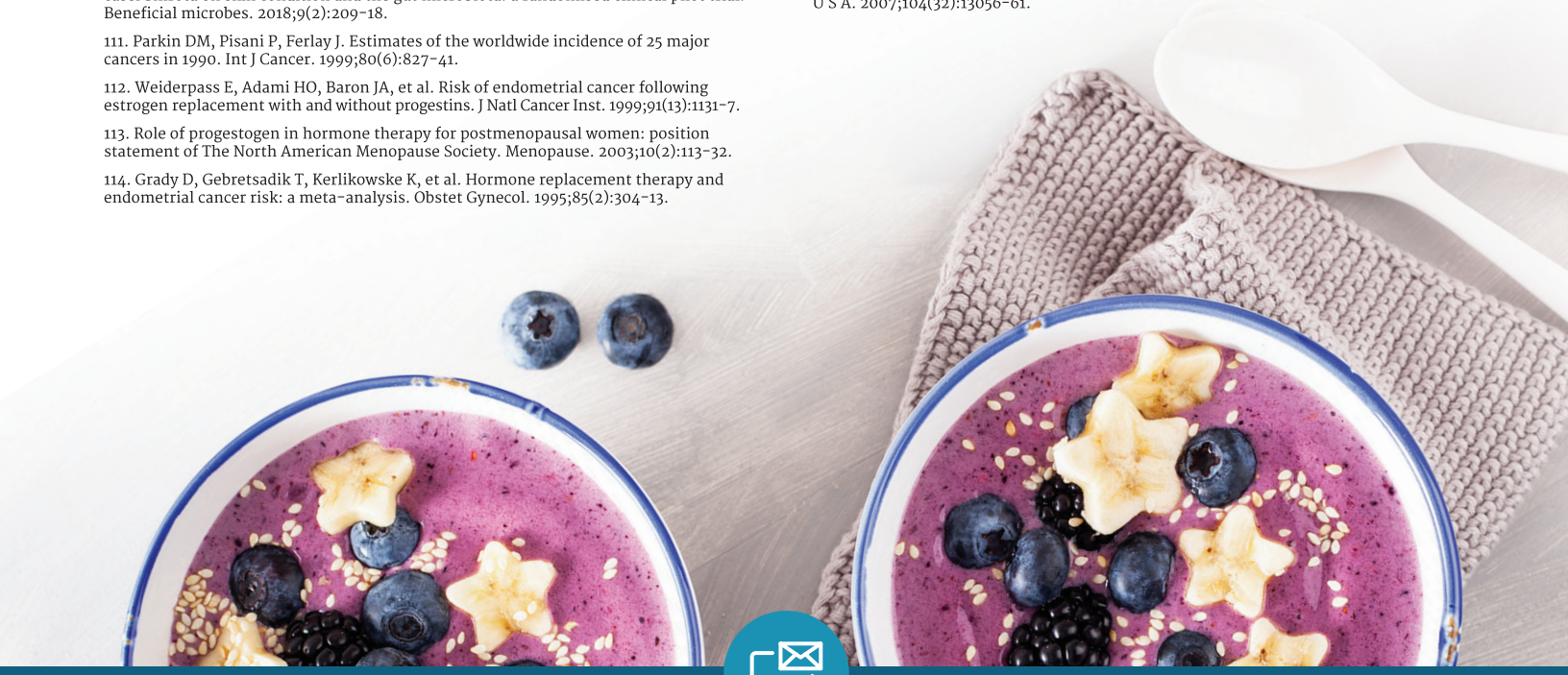
120. Kurzer MS. Hormonal effects of soy in premenopausal women and men. J Nutr. 2002;132(3):570S-3S.

121. Vanegas JC, Afeiche MC, Gaskins AJ, et al. Soy food intake and treatment outcomes of women undergoing assisted reproductive technology. Fertil Steril. 2015;103(3): 749-55 e2.

122. Chavarro JE, Minguez-Alarcon L, Chiu YH, et al. Soy intake modifies the relation between urinary bisphenol A concentrations and pegnancy outcomes among women undergoing assisted reproduction. J Clin Endocrinol Metab. 2016;101(3):1082-90.

123. Muhlhauser A, Susiarjo M, Rubio C, et al. Bisphenol A effects on the growing mouse oocyte are influenced by diet. Biol Reprod. 2009;80(5):1066-71.

124. Dolinoy DC, Huang D, Jirtle RL. Maternal nutrient supplementation counteracts bisphenol A-induced DNA hypomethylation in early development. Proc Natl Acad Sci U S A. 2007;104(32):13056-61.



For more information visit SoyConnection.com or contact info@soyconnection.com

Soy Connection, on behalf of the United Soybean Board (USB), is a collaboration of health, nutrition and food industry experts with U.S. soybean farmers to educate on the benefits of U.S.-grown soy, including heart-healthy soybean oil and soyfoods. USB's 73 farmer-directors work on behalf of all U.S. soybean farmers to achieve maximum value for their soy checkoff investments. These volunteers invest and leverage checkoff funds in programs and partnerships to drive soybean innovation beyond the bushel and increase preference for U.S. soy. That preference is based on U.S. soybean meal and oil quality and the sustainability of U.S. soybean farmers. As stipulated in the federal Soybean Promotion, Research and Consumer Information Act, the USDA Agricultural Marketing Service has oversight responsibilities for USB and the soy checkoff.

UNITED SOYBEAN BOARD™

SoyConnection
By the United Soybean Board