International Research Journal of Medicine and Medical Sciences
Vol. 1(3), pp. 72-79, August 2013
Review

Use of soy isoflavones as alternative to hormonal therapy (HRT) for women in menopause: A review

Bhat Shabir[1]*, Raza A.[2], Paras Wani[3] and Shah Abuddin[4]

[1]D/O Ilmul Qabala, A & U Tibbia College and Hospital, Karol Bagh, New Delhi, India.
[2]A & U Tibbia College and Hospital, Karol Bagh, New Delhi, India.
[3]D/O Saidla, A & U Tibbia College and Hospital, Karol Bagh, New Delhi, India.

Accepted 1 August, 2013

ABSTRACT

Menopause is a complex and multifaceted phenomenon, one that is very challenging to study for a number of reasons. Menopause involves multiple domains, including physiological as well as psychological and lifestyle changes. The loss of estrogen following menopause has several effects, not only physically, but also psychologically. Whether to take hormone replacement therapy (HRT) is one of the major decisions women during menopause or early menopause have to make. The overwhelming majority will decide against it, either out of fear of potential risks or simply to avoid unpleasant side effects. The main objective of this review paper was to investigate the effects of isoflavones in women during menopause on the hot flashes, bone mass, breast, cardiovascular diseases. Epidemiologic and clinical data suggest that soy foods can make important contributions to the health of women, particularly postmenopausal women. Soy foods potentially reduce coronary heart disease through multiple mechanisms and may be especially beneficial when consumed by young postmenopausal women.

Keywords: Menopause, hormone replacement therapy, soy isoflavones, bone health, cardiovascular disease.

*Corresponding author. E-mail: drbhatshabir55@gmail.com.

INTRODUCTION

Menopause is the cessation of menstruation. Operationally, it is defined as the absence of menstruation for a year (Nussey and Whitehead, 2001). The term menopause or premenopausal is defined by the World Health Organization (WHO) as the two to eight years prior to menopause and one year following final menses. Natural menopause is a result from the loss of ovarian follicular activity (WHO, 1990). Menopause involves multiple domains including physiological as well as psychological and lifestyle changes.

The loss of estrogen following menopause has several effects, not only physically but also psychologically. Some of the effects are limited to the transition period when a woman is adjusting to the loss of her hormones, such as menstrual periods becoming irregular (Nussey and Whitehead, 2001). Other changes may occur first at the actual menopause, but may have serious consequences in the long term. Some of the deleterious effects of lowered estrogen levels, include reduction of bone mass, menopausal symptoms, and hypercholesterolemia (Somekawa et al., 2001). Osteoporosis is one of the most common endocrine diseases and occurs when the bone resorption exceeds the bone formation. The bone loss is accelerated for several years after the withdrawal of estrogens at menopause (Nussey and Whitehead, 2001). Epidemiologically, women appear to be protected against cardiovascular disease by their sex hormones (Nussey and Whitehead, 2001) and incidence of cardiovascular disease has been shown to increase substantially after menopause (Wroblewski and Cooke, 2000). This adverse effect of menopause has been attributed to the metabolic effect of the loss of estrogen increasing the atherogenic potential of circulating lipids leading to coronary artery disease and stroke (Nussey and Whitehead, 2001)

Many studies have been conducted to assess role of

soy in menopausal sympyoms. With this preview, this review was done to analyse the role of soy in management of menopausal symptoms instead of conventional treatment.

LITERATURE REVIEW

An intensive literature review was done regarding HRT and soy isoflavins and their role in menopausal symptoms was compared. Medline and pubmed databases were searched from January 2000 to October 2012, using a detailed list of terms related to botanicals and menopausal symptoms. Studies were reviewed and analysed for the efficacy of soy in menopausal symptoms.

Hormone replacement therapy

Hormone replacement therapy (HRT) refers to a variety of treatments involving different estrogens and progestins. HRT may be used during a short period of time to alleviate menopausal symptoms, such as hot flushes and vaginal atrophy HRT may also be used for several years or more to prevent changes in bone density and reduce the risk of cardiovascular disease. However, when HRT is stopped, the same physiological changes that accompany the untreated menopause still occur (Nussey and Whitehead, 2001), but later in life even if hormone replacement therapy is widely used with evident success in menopausal women, approximately 70% drop out after the first year of treatment. Reasons for dropping out were irregular bleeding, breast discomfort, nausea, migraine, weight gain, water retention, besides the fear of breast cancer Over the last few years, there has been a debate about HRT safety particularly with regard to the risk of developing breast cancer, but also the increased risk of endometrial cancer (Nussey and Whitehead, 2001; Elkind-Hirsch, 2001).

A randomized, double blind placebo-controlled trial from the Women's Health Initiative (WHI) showed an increase in both cardiovascular disease and breast cancer (Writing group for the Women's Health Initiative investigators, 2002). Some women may also not be able to treat their menopausal problems with HRT as they have absolute contraindications such as undiagnosed vaginal bleeding, active thromboembolic disease and active breast or endometrial cancer (Hersh et al., 2004). Concerns about the risks of conventional HRT have led increasingly more women and their practitioners to seek alternative therapies (Wroblewski and Cooke, 2000).

Overview of isoflavones

Isoflavones have a limited distribution in nature. In fact, diets that do not include soy foods are almost devoid of these compounds (Franke et al., 1998). Not surprisingly, whereas average isoflavones intake among adults ranges from about 30 to 50 mg/day in Japan and Chinese cities such as Shanghai (Messina et al., 2006), intake is less than 3 mg/day in the United States and other Western countries (Horn-Ross et al., 2003; Goodman-Gruen and Kritz-Silverstein, 2001; De Kleijn et al., 2001; Van Erp-Baart et al., 2003; Van der Schouw et al., 2005; Boker et al., 2002). Using weighted, 2-day food consumption data for the U.S. population from the National Health and Nutrition Examination Survey (NHANES) 2007 to 2008, the United States Department of Agriculture recently estimated that daily per capita isoflavone intake is 0.68 mg/day (Haytowitz and Bhagwat, 2012). Isoflavones occur in soybeans as glycosides (a sugar molecule is attached to the isoflavone backbone) (Murphy et al., 2002) upon ingestion, the sugar is hydrolyzed thereby allowing absorption to occur (Rowland et al., 2003). In fermented soy foods such asmiso, tempeh and natto, substantial amounts of the isoflavones occur asaglycones due to bacterial hydrolysis. The three isoflavones genistein, daidzein and glycitein and their respective glycosides account for approximately 50 percent, 40 and 10%, respectively, of the total isoflavone content of soybeans (Murphy et al., 2002). Each gram of soy protein in soybeans and traditional soy foods is associated with approximately 3.5 mg of isoflavones (Messina et al., 2006). In this document, isoflavone amounts are expressed in a glycone equivalent weights. Consequently, one serving of a traditional soyfood, such as 3 to 4 oz of tofu or 1 cup of soymilk, typically provides about 25 mg of isoflavones.

Soy protein is present in a wide range of commonly consumed foods in the U.S. However, isoflavones 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, oxidation inhibition and improved texture. And second, the isoflavone concentration of the soy protein used in this way is generally quite low in comparison to traditional soy foods. The isoflavone-to-protein ratio noted above for traditional soy foods does not apply to many processed forms of soy.

More and more women rely on phytoestrogens, or plant estrogens, such as isoflavones to tailor their menopausal therapy in a "natural" way Isoflavones may be classed as natural selective estrogen receptor modulators (SERMs) (Carusi, 2000) that exert selective estrogenic effects (e.g. on bone and plasma lipids) and anti-estrogenic effects or no effect on tissues where estrogen stimulation may be undesirable (e.g. breast and endometrium) (Nussey and Whitehead, 2001).

Asian people consume 10 to 100 times more isoflavones than Western people (Barnes et al., 1995) and it has been shown that Japanese women experience

fewer hot flushes (Lock, 1991), contested fewer hip fractures (Cooper et al., 1992) and a decreased rate of hormone-dependent cancers (Parkin, 1989) in comparison to American women. Phytoestrogens are diphenolic compounds that structurally resemble human estrogens (Hurst, 2002).

Isoflavones are diphenolic compounds with a chemical structure similar to the hormone estrogen; they bind to both estrogen receptors alpha and beta – ERα and ERβ, (Carlsson et al., 1997; Kuiper et al., 1998). For this reason, they are commonly referred to as phytoestrogens.

In the 1960s, the existence of a protein responsible for specific binding of 17β-estradiol in the uterus was recognized (Jensen and Jacobson, 1962). In 1996, a novel estrogen receptor was discovered in the rat prostate. It was named estrogen receptor β (ER-β) to distinguish it from the previously cloned estrogen receptor α (ER-α) (Kuiper et al., 1996). These two known estrogen receptors ER-α and ER-β may play different roles in gene regulation (Paech et al., 1997).

With this preview, review was done so as to assess the effects of Soy in women during menopause. The main objective of this review paper was to investigate the effects of isoflavones in women during menopause on the: 1. Hot flashes; 2. bone mass; 3. breast; 4. cardiovascular disease.

Hot flashes

Hot flashes are the most common reason given by women seeking treatment for menopausal symptoms. For the majority of women who experience them, hot flashes begin before to menopause. 10 to 15% of these women experience hot flashes that are severe and frequent (Kronenberg, 1990). Although hot flashes usually subside after six months two-year (Berg et al., 1988), many women report having them for up to 20 years after menopause (Rodstrom et al., 2002). The etiology of hot flashes is not fully understood but the drop in circulating estrogen levels that occurs during menopause is 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 (Adlercreutz et al., 1992). Even Chinese-American and Japanese-American women are about one-third less likely to report experiencing hot flashes than Caucasian women (Gold et al., 2000). Interestingly, among Asian women, chilliness and shoulder aches are much more commonly reported menopausal symptoms than hot flashes. Recent evidence suggests, however, that Japanese women are reluctant to report having hot flashes (Maki et al., 2009). To this point, one study found that hot flash frequency was lower among Japanese compared to Caucasian women when based on a subjective determination (personal diary), but not when determined objectively by measuring sternal and nuchal skin conductance (Brown et al., 2009). Asian women have considerably fewer menopausal symptoms than Western women, and it has been hypothesized that this difference is due to their high intake of isoflavones (Adlercreutz et al., 1992). It was found that adding 45 g of soy flour to the diet of post menopausal women significantly decreased the reporting of hot flashes by 40%. Interestingly, in the same trial, it was found that consuming 45 g of wheat flour significantly decreased the rate of hot flashes by 25% (Murkies et al., 1995; Messina and Hughes, 2006), more than 50 clinical trials have examined the impact of isoflavones-rich soy foods or isoflavones supplements on the alleviation of menopause-related hot flashes. In recent years, investigators have gravitated toward the use of supplements rather than soy foods to enhance compliance and reduce the complexity of study design. The results of these trials have produced inconsistent results. Although some recent reviews and analyses of the literature have concluded that isoflavone-rich products alleviate hot flashes (Howes et al., 2006). One of the studies showed that consumption of a soy protein drink significantly decreased hot flash rate (Harding et al., 1996). Three of the studies did not show any significant effects of soy on hot flash rate (Burke, 1996; Dalais, 1997; Kronenberg and Wade, 1997). However, in one study, it was noted that soy modestly reduced the severity of menopausal symptoms and in other study researcher found significant increase in vaginal cytology maturation. A more recent study by Brezinski found that a significant decrease in the hot flash rate along with decreased vaginal dryness occurred with consumption of a diet containing products such as tofu, miso linseed, and soy beverages. The mechanism by which isoflavones may ease vasomotor symptoms, like hot flushes, is by acting as weak estrogen agonists. In a low-estrogen environment, as in a postmenopausal woman, isoflavones will exhibit their most potent estrogenic effects (Brezinski et al., 1997).

In a study of 180 Japanese women given a standardized questionnaire to evaluate the severity of menopausal symptoms, only 5% reported symptoms of hot flushes (Uchiyama and Ueno, 2001).

In a community-based study, the incidence of hot flushes was inversely related both to the amount of soy foods consumed and the daily intake of isoflavones; thus, there is indirect evidence for a role for isoflavones (Nagata et al., 2001).

A large number of clinical trials have reported a decrease in hot flushes in women treated with soy protein, however many of these trials fail to prove that soy is superior to placebo (Kang et al., 2002).

Numerous intervention studies using isoflavone extract have showed inconsistent results, with some reporting significantly fewer hot flushes, whereas others report no significant effects secondary to an apparent placebo

effect. The potential for phytoestrogens to alleviate menopausal hot flushes is an area of active research (Duncan et al., 2003).

A recent meta-analysis of 17 randomized, controlled, parallel group studies that had compared isoflavones therapy (using either soy products or red clover products) to a non-isoflavone, non-estrogenic comparator, suggest that isoflavone supplementation may produce a slight to modest reduction in the number of daily flushes in menopausal women and that the benefit may be more apparent in women experiencing a high number of flushes (Howes et al., 2006).

Cardiovascular disease

Coronary artery disease (CAD) is the most common cause of mortality for women and increases dramatically after menopause (Wroblewski and Cooke, 2000).

A high blood concentration of low-density lipoprotein (LDL) is an established risk factor for cardiovascular disease (Ballantyne, 1998).

Women have more favorable lipoprotein profiles than men starting in adolescence. At the time of menopause, however, adverse changes in lipoprotein profiles occur, including increases in total and LDL cholesterol, decrease in high-density lipoprotein (HDL), and shift in LDL particle size toward smaller, denser particles. These adverse changes have been attributed to the changes in estrogen levels that occur at the time of menopause (Bittner, 2002).

Epidemiologic data have shown that women ingesting high amounts of phytoestrogens from soy products have less cardiovascular disease, than those eating Western diets (Dewell et al., 2006).

Soy, and especially the isoflavones contained in soy, has been suggested to improve lipoprotein levels, thus reducing the risk of CAD. However, this hypothesis is not uniformly accepted (Anderson et al., 1995). Pivotal paper in this field is an often cited meta-analysis of 38 controlled clinical trials of soy consumption in humans. Improvements in total cholesterol by 9.3% and LDL by 12.9%, as well as a decrease in triglyceride levels of 10.5% were revealed. The average intake of soy was 47 g/day in these trials. The extent of reduction was dependent upon the initial serum cholesterol concentrations. In subjects with moderate hypercholesterolemia, a decrease in total cholesterol of 7.4% was observed, whereas subjects with severe hypercholesterolemia achieved a decline of 19.6%. In the majority of 22 randomized trials, isolated soy protein with isoflavones decreased LDL cholesterol concentrations. The average effect was approximately 3%, as compared with milk or other proteins. The reduction is considered small relative to the large amount of soy protein tested in these studies, averaging 50 g, which is about half the usual total daily protein intake in the US. Most recent studies favor soy protein rather than soy isoflavones as the responsible nutrient although it cannot be ruled out that another component in soybeans could be the active factor Sacks and Dewell noted that “the changes reported in studies using purified isoflavones supplements, although not statistically significant, are quantitatively similar to those observed in the soy protein studies”. Many studies during the past 10 years have not confirmed earlier research indicating that soy protein has clinically important favorable effects on LDL cholesterol and other cardiovascular disease risk factors, as compared with other proteins. However, because of soy products high content of polyunsaturated fats, fiber, vitamins, and minerals and low content of saturated fat, it still should be beneficial to cardiovascular and overall health (Sacks et al., 2006).

Dietary isoflavones have also been attributed cardio-protective benefits beside the reduction in LDL cholesterol, including an inhibition of pro-inflammatory cytokines, cell adhesion proteins and inducible nitric oxide production, potential reduction in the susceptibility of the LDL particle to oxidation, inhibition of platelet aggregation and an improvement in vascular reactivity. Increasing number of studies reveal a significant impact of genetic variation on changes in cardiovascular risk factors in response to dietary intervention. This might explain some of the differences in the current literature concerning isoflavones and cardiovascular health (Rimbach et al., 2007).

Soy foods potentially offer protection against heart disease through several different mechanisms. Soy foods are low in saturated and high in polyunsaturated fat (Slavin et al., 2009).

In addition, soy protein directly lowers blood cholesterol levels, an attribute that was formally recognized by the U.S. Food and Drug Administration in 1999 (Food labeling: health claims; soy protein and coronary heart disease, 1999).

Estimates are that, via the fatty acid profile and soy protein content, when soy foods replace conventional sources of protein in Western diets, blood low-density-lipoprotein (LDL) cholesterol levels will be lowered by about 8%. In theory, over a period of years, this may reduce risk of coronary heart disease (CHD) by 8 to 16% (Jenkins et al., 2010).

There is also evidence that, independent of effects on blood cholesterol, soyfoods may reduce CHD risk. For example, four recently published meta-analyses found that soy lowered blood pressure (Hooper et al., 2008; Dong et al., 2011; Liu et al., 2012; Taku et al., 2010).

Lastly, the most important study came from the Women’s Isoflavones Soy Health (WISH). This 3-year study involved 350 healthy postmenopausal women ages 45 to 92, and found that isoflavones-rich soy protein inhibited the progression of subclinical atherosclerosis (Hodis et al., 2011).

Among 45 to 60 year old Americans, approximately

three times as many men will have a heart attack as compared to women. However, by the age of 65, rates of coronary heart disease become more similar for men and women. The decrease in estrogen with the onset of menopause is thought to be the major factor accounting for this catch-up" by women in regard to heart disease (Wu et al., 2009).

Arising from the epidemiological studies showing significantly lower rates of heart disease in Asian countries, attention has focused on identifying the differences that may contribute to such disparities. For almost twenty years, small studies examining the role of soy protein in lowering cholesterol have been conducted on both humans and animals (Peng et al., 2009; Messina and Hilakivi-Clarke, 2009). Animal studies have established that consumption of soy protein in place of animal protein leads to a decrease in serum cholesterol concentration (Mishra et al., 2011).

Anderson, John stone and Cook-Newell in1995 conducted a meta-analysis examining the effects of soy protein intake on serum lipid profiles. The study, which included analysis of 38 controlled clinical trials, found a reduction in serum total cholesterol ranging from a non significant 3.3% in normo-cholesterolemic individuals (initial values below 200 mg per deciliter),a non-significant 4.4% in mild hypercholesterolemic individuals (initial values of 200 to 255 mg per deciliter), a significant 7.4% in moderate hypercholesterolemic individuals (initial values of 259 to 333 mg per deciliter), to a significant 19.6% in severely hypercholesterolemic individuals (above 335 mg per deciliter). Regression analysis indicated that changes in serum lipid concentrations were independent of changes in body weight or dietary intake of total fat, saturated fat and cholesterol. In those individuals already consuming a low-fat diet, consumption of soy-containing products further reduced low density lipoprotein (LDL) cholesteroletary intake of total fat, saturated fat and cholesterol levels. These results suggest that soy may serve as a beneficial addition to a traditional cholesterol-lowering diet by further reducing serum cholesterol.

The researchers concluded that a daily consumption of 31 to 47 g of soy protein has the potential to significantly decrease serum and LDL cholesterol. In addition, the study showed a non-significant 2.4% increase in serum high-density lipoprotein (HDL) cholesterol (Russo et al., 2005).

Breast

At the beginning of the 1980s, it was proposed that isoflavonoids may prevent breast cancer. This was the starting point of numerous epidemiological, experimental, case-control and prospective studies investigating the hypothesis (Doyle et al., 2006).

Epidemiological observations show that Asian women have significantly lower risk of breast cancer compared with Western women (Parkin, 1989).

Studies assessing cancer risk and diet have provided support for the theory that high intake of isoflavone-rich soy contributes to this risk difference. The findings of these studies showed significant inverse associations between breast cancer and soy isoflavones, both in relation to their consumption and their urinary excretion (Duncan et al., 2003).

Observations that Asian women who emigrate to the U.S. and adopt Western diet lose their lower risk of breast cancer further support the hypothesis that isoflavones may prevent breast cancer (Ziegler et al., 1993).

In the Asian countries, the diets are also low in fat and red meat and are often rich in fish, elements that have independently been linked to a decreased cancer risk (Adlercreutz, 2002). Tamoxifen is a selective estrogen receptor modulator (SERM) used clinically in the adjuvant treatment of estrogen-dependent breast cancer. Individuals at high risk of developing breast cancer are also administered tamoxifen as a prophylactic. Therapies using tamoxifen is associated with menopausal symptoms such as hot flushes, joint pain, sleep disorders and depression, which may be reduced by the use of HRT. However long-term use of HRT for breast cancer patients is discouraged as HRT is associated with an increased risk for mammary carcinogenesis (Limer and Speirs, 2004).

Soy isoflavones supplements may be used as a natural alternative to alleviate the tamoxifen-induced menopausal symptoms (Wuttke et al., 2002).

Messina and Loprinzi, in 2001, concluded in their review that "the data are not impressive that the adult consumption of soy affects the risk of developing breast cancer or that soy consumption affects the survival of breast cancer patients. Consequently, if breast cancer patients enjoy soy products, it seems reasonable for them to continue to use them".

Charles Simone, M.D., author of Breast Health (Avery, 1995), discourages his breast cancer patients from eating any soy foods because their effect on active cancers is not known (Simone, 1997). A recent meta-analysis found that, in Asian epidemiologic studies, higher soy intake was associated with a 29% decreased risk of breast cancer (Wu et al., 2008). However, there is solid evidence indicating that to derive this benefit, soy consumption must occur during childhood or adolescence (Lamartiniere et al., 2000; Shu et al., 2001; Wu et al., 2009). 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 (Wu et al., 2009; Peng et al., 2009; Messina and Hilakivi-Clarke, 2009).

This proposed mechanism may be similar to that proposed for the protective effect of early pregnancy

against breast cancer (Mishra et al., 2011).

The position of the American Cancer Society is that women with breast cancer can safely consume up to three servings of traditional soy foods daily (Russo et al., 2005).

CONCLUSION

Whether to take HRT is one of the major decisions women in per menopause or early menopause have to make. The overwhelming majority will decide against it, either out of fear of potential risks or simply to avoid unpleasant side effects. In fact, several studies have shown that only 15 to 20% of women will take HRT for more than a year, even women who do agree to take HRT frequently demonstrate poor compliance. But patients who decline HRT do need and will have other choices to help them weather vasomotor symptoms that can greatly disrupt their lives. Many women find these plant-based alternatives an important option that allows them to control their hot flushes without taking HRT. Soy foods are unique because they are rich dietary sources of isoflavones, which are endocrine active substances but different from the hormone estrogen. Epidemiologic and clinical data suggest that soy foods can make important contributions to the health of women, particularly postmenopausal women. Soy foods potentially reduce coronary heart disease through multiple mechanisms and may be especially beneficial when consumed by young postmenopausal women. Clinical research indicates that isoflavones alleviate hot flashes although the evidence that they reduce bone loss is unimpressive. Nevertheless, soy foods 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. As there remains a controversy over whether soy foods are contraindicated for breast cancer patients, the clinical evidence indicates that neither soy foods nor isoflavones adversely affect breast tissue. Recent epidemiologic evidence indicates that soy consumption improves the prognosis of breast cancer patients.

REFERENCES

Adlercreutz H, 2002. Phytoestrogens and cancer. The Lancet Oncol, 3:364-373

Adlercreutz H, Hamalainen E, Gorbach S, Goldin B, 1992. Dietary phyto-oestrogens and the menopause in Japan. Lancet, 339:1233.

Anderson JW, Johnstone BM, Cook-Newell ME, 1995. Meta-analysis of the effects of soy protein intake on serum lipids. New England J Med, 333:276-282

Ballantyne CM, 1998. Low-density lipoproteins and risk for coronary artery disease. Am J Cardiol, 82:3Q-12Q

Barnes S, Peterson TG, Coward L, 1995. Rationale for the use of Genistein-containing soy matrices in chemoprevention trials for breast and prostate cancer. J Cell Biochem, 22: 181-187.

Berg G, Gottwall T, Hammar M, Lindgren R, Gottgall T, 1988. Climacteric symptoms among women aged 60-62 in Linkoping, Sweden, in 1986. Maturitas, 10:193-199.

Bittner V, 2002. Lipoprotein abnormalities related to women's health. Am J Cardiol, 90(suppl):77i-84i

Boker LK, Van der Schouw YT, De Kleijn MJ, Jacques PF, Grobbee DE, Peeters PH, 2002. Intake of dietary phytoestrogens by Dutch women. J Nutr, 132: 1319-1328.

Brezinski A, Adlercreutz H, Shmueli A, Shaoul R, Reosler A and Schenker JG, 1997. Short-term effects of phytoestrogen-rich diet on postmenopausal women. J North Am Menopause Soc, 4:89-94

Brown DE, Sievert LL, Morrison LA, Reza AM, Mills PS, 2009. Do Japanese American women really have fewer hot flashes than European Americans? The Hilo Women's Health Study. Menopause, 16:870-876

Burke GL, 1996. The potential use of a dietary soy supplement as a post menopausal hormone replacement therapy. [On-line]. Second International Symposium on the Role of Soy in Preventing and Treating Chronic Disease. Available:http://soyfoods.com/symposium/0a6b2.html.

Carlsson B, Grandien K, Enmark E, Haggblad J, Nilsson S, Gustafsson JA, 1997. Comparison of the ligand binding specificityand transcript tissue distribution of estrogen receptors alpha and beta. Endocrinology, 138: 863-870.

Carusi D, 2000. Phytoestrogens as hormone replacement therapy: an evidenced-based approach. Primary Care Update for Ob/Gyns, 7:253-259.

Cooper C, Campion G, Melton LJ, 1992. Hip fractures in the elderly: A world-wide projection. Osteoporos Int, 2:285-289.

Dalais FS, 1997. Soy and menopause. The Soy Connection, 5(4):1-4.

De Kleijn MJ, van der Schouw YT, Wilson PW, Adlercreutz H, Mazur W, Grobbee DE, Jacques PF, 2001. Intake of dietary phytoestrogens is low in postmenopausal women in the United States: The Framingham study (1-4). J Nutr, 131:1826-1832.

Dewell A, Hollenbeck PLW, Hollenbeck CB, 2006. Clinical review: A critical evaluation of the role of soy protein and isoflavone supplementation in the control of plasma cholesterol concentration. J Clin Endocrinol Metab, 91:772-780

Dong JY, Tong X, Wu ZW, Xun PC, He K, Qin LQ, 2011. Effect of soya protein on blood pressure: a meta-analysis of randomised controlled trials. Br J Nutr, 106:317-326.

Doyle C, Kushi LH, Byers T, Courneya KS, Demark-Wahnefried W, Grant B, McTiernan A, Rock CL, Thompson C, Gansler T, Andrews KS, 2006. Nutrition and physical activity during and after cancer treatment: An American cancer society guide for informed choices. CA Cancer J Clin, 56:323-353.

Duncan AM, Phipps WR, Kurzer MS, 2003. Phyto-oestrogens. Best Pract Res Clin Endocrinol Metab, 17(2):253-271.

Elkind-Hirsch K, 2001. Effect of dietary phytoestrogens on hot flushes: Can soy-based proteins substitute for traditional estrogen replacement therapy? Menopause, 8:154-156.

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

Franke AA, Custer LJ, Wang W, Shi CY, 1998. HPLC analysis of isoflavonoids and other phenolic agents from foods and from human fluids. Proc Soc Exp Biol Med, 217:263-273.

Gold EB, Sternfeld B, Kelsey JL, Brown C, Mouton C, Reame N, Salamone L, Stellato R, 2000. Relation of demographic and lifestyle factors to symptoms in a multi-racial/ethnic population of women 40-55 years of age. Am J Epidemiol, 152:463-473.

Goodman-Gruen D, Kritz-Silverstein D, 2001. Usual dietary isoflavone intake is associated with cardiovascular disease risk factors in postmenopausal women. J Nutr, 131:1202-1206.

Harding C, Morton M, Gould V, McMichael PD, Howell A and Bundred NJ, 1996. Dietary soy supplementation is oestrogenic in menopausal women. [On-line]. Second International Symposium on the Role of Soy in Preventing and Treating Chronic Disease. Available:http://soyfoods.com/symposium/pa7.html.

Haytowitz DB, Bhagwat S, 2012. Assessment of sources and dietary intake of isoflavones in the U.S. diet (poster presentation). 9th

international symposium on the role of soy in health promotion and chronic disease prevention and treatment (Washington, DC, USA).
Hersh AL, Stefanik ML, Stafford RS, 2004. National use of postmenopausal hormone therapy. Annual trends and response to recent evidence. J Am Med Assoc, 291:47-53.
Hodis HN, Mack WJ, Kono N, Azen SP, Shoupe D, Hwang-Levine J, Petitti D, Whitfield-Maxwell L, Yan M, Franke AA, Selzer RH, 2011. Isoflavone soy protein supplementation and atherosclerosis progression in healthy postmenopausal women: a randomized controlled trial. Stroke, 42:3168-3175.
Hooper L, Kroon PA, Rimm EB, Cohn JS, Harvey I, Le Cornu KA, Ryder JJ, Hall WL, Cassidy A, 2008. Flavonoids, flavonoid-rich foods, and cardiovascular risk: A meta-analysis of randomized controlled trials. Am J Clin Nutr, 88:38-50.
Horn-Ross PL, John EM, Canchola AJ, Stewart SL, Lee MM, 2003. Phytoestrogen intake and endometrial cancer risk. J Nat Cancer Inst; 95: 1158-64.
Howes LG, Howes JB, Knight DC, 2006. Isoflavone therapy for menopausal flushes: a systematic review and meta-analysis. Maturitas, 55:203-211.
Hurst JW, 2002. Methods of analysis for functional foods and nutraceuticals. CRC Press, Florida, USA.
Jenkins DJ, Mirrahimi A, Srichaikul K, Berryman CE, Wang L, Carleton A, Abdulnour S, Sievenpiper JL, Kendall CW, Kris-Etherton PM, 2010. Soy protein reduces serum cholesterol by both intrinsic and food displacement mechanisms. J Nutr, 140:2302S-2311S.
Jensen EV, Jacobson HI, 1962. Basic guides to the mechanism of estrogen action. Recent Prog Horm Res, 18:387-414.
Kang HJ, Ansbacher R, Hammoud MM, 2002. Use of alternative and complementary medicine in menopause. Int J Gynecol Obstet, 79:195-207.
Kronenberg F, 1990. Hot flashes: Epidemiology and physiology. Ann N Y Acad Sci, 592:52-86; Discussion, 123-33.
Kronenberg F, Wade C, 1997. Hot flashes and HRT. The Soy Connect, 5(4), 2.
Kuiper GG, Lemmen JG, Carlsson B, Corton JC, Safe SH, van der Saag PT, van der Burg B, Gustafsson JA, 1998. Interaction of estrogenic chemicals and phytoestrogens with estrogen receptor beta. Endocrinology, 139:4252-4263.
Kuiper GGJM, Enmark E, Pelto-Huikko M, Nilsson S, Gustafsson JÅ, 1996. Cloning of a novel estrogen receptor expressed in rat prostate and ovary. Proceedings of the National Academy of Sciences, 93:5925-5930.
Lamartiniere CA, Zhao YX, Fritz WA, 2000. Genistein: mammary cancer chemoprevention, in vivo mechanisms of action, potential for toxicity and bioavailability in rats. J Women's Cancer, 2:11-19.
Limer JL, Speirs V, 2004. Phyto-oestrogens and breast cancer chemoprevention. Breast Cancer Res, 6:119-127
Liu XX, Li SH, Chen JZ, Sun K, Wang XJ, Wang XG, Hui RT, 2012. Effect of soy isoflavones on blood pressure: A meta-analysis of randomized controlled trials. Nutr Metab Cardiovasc Dis, 22: 463-470.
Lock M, 1991. Contested meanings of the menopause. The Lancet. 337:1270-1272.
Maki PM, Rubin LH, Fornelli D, Drogos L, Banuvar S, Shulman LP, Geller SE, 2009. Effects of botanicals and combined hormone therapy on cognition in postmenopausal women. Menopause, 16:1167-1177.
Messina M, Hilakivi-Clarke L, 2009. Early intake appears to be the key to the proposed protective effects of soy intake against breast cancer. Nutr Cancer, 61:792-798.
Messina M, Hughes C 2003. Efficacy of soyfoods and soybean isoflavone supplements for alleviating menopausal symptoms is positively related to initial hot flush frequency. J Med Food, 6:1-11.
Messina M, Nagata C, Wu AH, 2006. Estimated Asian adult soy protein and isoflavone intakes. Nutr Cancer, 55:1-12.
Messina MJ, Loprinzi CL. 2001. Soy for breast cancer survivors: a critical review of the literature. J Nutr 131: 3095S–3108S.
Mishra P, Kar A, Kale RK, 2011. Prepubertal daidzein exposure enhances mammary gland differentiation and regulates the expression of estrogen receptor-alpha and apoptotic proteins. ISRN oncology, 896826.
Murkies AL, Lombard C, Strauss BJD, Wilcox G, Burger HG, Morton MS, 1995. Dietary flour supplementation decreases postmenopausal hot flushes: effect of soy and wheat. Maturitas, 21:189-195.
Murphy PA, Barua K, Hauck CC, 2002. Solvent extraction selection in the determination of isoflavones in soy foods. J Chromatogr B Analyt Technol Biomed Life Sci, 777:129-138.
Nagata C, Takatsuka N, Kawakami N, Shimizu H, 2001. Soy product intake and hot flashes in Japanese women: Results from a community-based prospective study. Am J Epidemiol, 153:790-793.
Nussey S, Whitehead S, 2001. Endocrinology: An integrated approach. BIOS Scientific Publishers Limited, Oxford, UK.
Paech K, Webb P, Kuiper GGJM, Nilsson S, Gustafsson JÅ, Kushner PJ, Scanlan TS, 1997. Differential ligand activation of estrogen repectors ERα and ERβ at AP1 sites. Science, 277:1508-1510.
Parkin DM, 1989. Cancers of the breast, endometrium and ovary: geographic correlations. European J Cancer Clin Oncol, 25:1917-1925.
Peng JH, Zhang F, Zhang HX, Fan HY, 2009. Prepubertal octylphenol exposure up-regulate BRCA1 expression, down-regulate ER alpha expression and reduce rat mammary tumorigenesis. Cancer Epidemiol, 33:51-55.
Peng JH, Zhang F, Zhang HX, Fan HY, 2009. Prepubertal octylphenol exposure up-regulate BRCA1 expression, down-regulate ER alpha expression and reduce rat mammary tumorigenesis. Cancer Epidemiol, 33:51-55.
Rimbach G, Boesch-Saadatmandi C, Frank J, Fuchs D, Wenzel U, Daniel H, Hall WL, Weinberg PD, 2007. Dietary isoflavones in the prevention of cardiovascular disease: A molecular perspective. Food and Chemical Toxicology. Article in press; doi:10.1016/j.fct.2007.06.029.
Rodstrom K, Bengtsson C, Lissner L, Milsom I, Sundh V, Bjorkelund CA, 2002. longitudinal study of the treatment of hot flushes: the population study of women in Gothenburg during a quarter of a century. Menopause, 9:156-161.
Rowland I, Faughnan M, Hoey L, Wahala K, Williamson G, Cassidy A, 2003. Bioavailability of phyto-oestrogens. Br J Nutr, 89 Suppl1:S45-58
Russo J, Mailo D, Hu YF, Balogh G, Sheriff F, Russo IH, 2005. Breast differentiation and its implication in cancer prevention. Clin Cancer Res, 11:931S-936S.
Sacks FM, Lichtenstein A, Van Horn L, Harris W, Kris-Etherton P, Winston M, 2006. Soy protein, isoflavones, and cardiovascular health: An American heart association science advisory for professionals from the nutrition committee. Circulation, 113:1034-1044.
Shu XO, Jin F, Dai Q, Wen W, Potter JD, Kushi LH, Ruan Z, Gao YT, Zheng W, 2001. Soyfood intake during adolescence and subsequent risk of breast cancer among Chinese women. Cancer Epidemiol Biomarkers Prev, 10:483-488.
Simone CB, 1997. Breast cancer : nutrition and lifestyle modification to augment oncology care. 26th Annual Nutritional Medicine Today Conference; Apr 18-20; Toronto, Ontario, Canada.
Slavin M, Kenworthy W, Yu LL, 2009. Antioxidant properties, phytochemical composition and antiproliferative activity of Maryland-grown soybeans with colored seed coats. J Agric Food Chem, 57:111740-85.
Somekawa Y, Chiguchi M, Ishibashi T, Aso T, 2001. Soy intake related to menopausal symptoms, serum lipids, and bone mineral density in postmenopausal Japanese women. Obstet Gynecol, 97(1):109-115.
Taku K, Lin N, Cai D, Hu J, Zhao X, Zhang Y, Wang P, Melby MK, Hooper L, Kurzer MS, Mizuno S, Ishimi Y, Watanabe S, 2010. Effects of soy isoflavone extract supplements on blood pressure in adult humans: systematic review and meta-analysis of randomized placebo-controlled trials. J Hypertens, 28:1971-1982.
Uchiyama S, Ueno T, Shirota T, 2001. The relationship between soy isoflavones and the menopausal symptoms in Japanese perimenopausal women. Ann Nutr Metab, 45:113 (abstract).
Van der Schouw YT, Kreijkamp-Kaspers S, Peeters PH, Keinan-Boker L, Rimm EB, Grobbee DE, 2005. Prospective study on usual dietary phytoestrogen intake and cardiovascular disease risk in Western women. Circulation, 111:465-471.
Van Erp-Baart MA, Brants HA, Kiely M, Mulligan A, Turrini A, Sermoneta C, Kilkkinen A, Valsta LM, 2003. Isoflavone intake in four different European countries: the VENUS approach. Br J Nutr, 89 Suppl 1: S25-30.
WHO Scientific Group on Research on the Menopause in the 1990s

1996. WHO Technical Report Series. No 866. Geneva, Switzerland.
Writing group for the Women's Health Initiative investigators, 2002. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. J Am Med Assoc, 288:872-881.
Wroblewski LL, Cooke JP, 2000. Phytoestrogens and cardiovascular health. J Am Col Cardiol, 35(6):1403-1410.
Wu AH, Yu MC, Tseng CC, Pike MC, 2008. Epidemiology of soy exposures and breast cancer risk. Br J Cancer, 98: 9-14.
Wu AH, Yu MC, Tseng CC, Pike MC, 2008. Epidemiology of soy exposures and breast cancer risk. Br J Cancer, 98:9-14.
Wu AH, Yu MC, Tseng CC, Stanczyk FZ, Pike MC, 2009. Dietary patterns and breast cancer risk in Asian American women. Am J Clin Nutr, 89:1145-1154.
Wuttke W, Jarry H, Westphalen S, Christoffel V, Seidlová-Wuttke D, 2002. Phytoestrogens for hormone replacement therapy? J Steroid Biochem Biol, 83:133-147.
Ziegler RG, Hoover RN, Pike MC, Hildesheim A, Nomura AMY, West DW, Wu-Williams AH, Kolonel LN, Horn-Ross PL, Rosenthal JF, Hyer MB, 1993. Migration patterns and breast cancer risk in Asian-American women. J Nat Cancer Inst, 85:1819-1827.