Safety and efficacy of soy and soy isoflavones in postmenopausal women

Laura Renee Rejent
The University of Toledo

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Safety and Efficacy of Soy and Soy Isoflavones in Postmenopausal Women

Laura Renee Rejent

The University of Toledo

2010
Dedication

Thank you to all my family for encouraging me through this long process and supporting me in my journey through this project. Your support and motivation has helped me all throughout this process.
Acknowledgements

Thank you Professor Gentry for all your help with this project. You have been there every step of the way with insight and help for my numerous questions. I know I could not have done this without you. Thank you.

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<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td>1</td>
</tr>
<tr>
<td>Methodology</td>
<td>2</td>
</tr>
<tr>
<td>Phytoestrogens</td>
<td>3</td>
</tr>
<tr>
<td>Menopause</td>
<td>7</td>
</tr>
<tr>
<td>Hormone Replacement Therapy</td>
<td>9</td>
</tr>
<tr>
<td>Cardiovascular Disease</td>
<td>10</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>13</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>15</td>
</tr>
<tr>
<td>Soy Isoflavone Safety</td>
<td>17</td>
</tr>
<tr>
<td>Breast Safety</td>
<td>20</td>
</tr>
<tr>
<td>Tamoxifen-Soy Safety</td>
<td>27</td>
</tr>
<tr>
<td>Soy Isoflavone Efficacy</td>
<td>31</td>
</tr>
<tr>
<td>Treatment and Prevention of Osteoporosis</td>
<td>31</td>
</tr>
<tr>
<td>Cardiovascular Protection</td>
<td>36</td>
</tr>
<tr>
<td>Prevention of Breast Cancer</td>
<td>39</td>
</tr>
<tr>
<td>Discussion</td>
<td>45</td>
</tr>
<tr>
<td>Limitations</td>
<td>52</td>
</tr>
<tr>
<td>Conclusion</td>
<td>54</td>
</tr>
<tr>
<td>References</td>
<td>56</td>
</tr>
<tr>
<td>Tables</td>
<td>61</td>
</tr>
<tr>
<td>Abstract</td>
<td>67</td>
</tr>
</tbody>
</table>
Introduction

Soy isoflavones have been suggested as a way to counteract the loss of estrogen linked to menopause because of their ability to bind and activate estrogen receptors. The estrogen loss associated with menopause causes many of the menopausal symptoms women experience after this change. Isoflavones have been studied for the prevention and treatment of bone loss in postmenopausal women, and for their potentially beneficial effects on the cardiovascular system and the breast. Debate over the efficacy of isoflavones to treat the aforementioned issues and inconsistent results have lead to uncertainty about the future of soy as a preventative or treatment tool for women’s health issues. Are soy isoflavones a reasonable alternative to HRT for these issues and how safe are soy isoflavones? This paper presents and analyzes the most recent findings about soy and its isoflavones in an attempt to answer these questions.
Methodology

The PubMed and CINAHL databases and Cochrane library were searched for meta-analyses, randomized controlled trials, crossover studies and cohort studies which used either or both premenopausal and postmenopausal women, and reported data on the use of soy products including isoflavones for women’s health issues including breast cancer risk. Studies were limited by language, only allowing for English language publications and preference was given to populations based in the United States and Asia as well as articles that were published between 2000 and 2010.

Search Terms

Structured electronic searches were carried out from December 2009 thru November 2010. Search terms included consisted of; soy foods, soy products, isoflavones, genistein, diadzein, premenopausal, postmenopausal, breast neoplasm, breast cancer, mammogram, and any combination of the aforementioned terms. In addition, each reference obtained was reviewed for citations or pertinent applicable articles which lend additional support to the aforementioned database searches.

Databases

The PubMed and CINAHL databases and the Cochrane library were searched.

Inclusion and exclusion criteria

First tier information consisted of meta-analyses, randomized controlled trials, and randomized crossover studies based in the US or Asia and published between 2000-2010 in English. Second tier data included cohort studies with populations based in the US or Asia and also published in English between 2000-2010. Third tier information consisted of all other studies in any population outside the US or prior to 2000.
Phytoestrogens

Phytoestrogens are compounds found in a variety of plants that when processed in the gastrointestinal tract have structural and functional similarities to estradiol. This similarity allows them to have estrogen-like effects on the body. Metabolism of phytoestrogens is variable because of the different sources, factors affecting the chemical composition of the natural food sources, and different processing mechanisms depending on the make-up of a person’s intestinal flora (Velentzis, Woodside, Cantwell, Leathem, & Keshtgar, 2008).

Phytoestrogens can be divided into three categories: isoflavones, ligans, and couestans. Isoflavones are the most potent type of phytoestrogen and are often associated with soy foods, but can also be found in a variety of legumes, as well as other sources (Kang, Ansbacher, & Hammoud, 2002). Isoflavones act like other phytoestrogens by acting similar to estradiol but unlike estradiol, isoflavones have both estrogenic and anti-estrogenic actions. These effects have been shown in vitro and in vivo. Isoflavones favor binding to beta estrogen receptors over alpha estrogen receptors (M. Messina & Wu, 2009). This preferential binding makes isoflavones appear to be a type of selective estrogen receptor modulator (SERM). The ability of isoflavones to bind at the beta receptors, producing a modest agonistic activity that is approximately one-third the potency of estradiol, and also have alpha estrogen receptor activity that is much weaker at approximately 0.001 the potency of estradiol, supports their inclusion as a type of selective estrogen modulator (Kang, et al., 2002).

There are three different types of isoflavones: diadzein, genistein, and glycitein. These isoflavones are found in two forms. The aglycone forms are diadzein, genistein, and glycitein and are found in fermented soy foods (Helferich, Andrade, & Hoagland, 2008). Their acetyl and malonylglucoside forms are called daidzin, glycitin and genistin and are found in whole non
fermented soy products. Soy foods are the most significant dietary source of isoflavones and the main isoflavone found in soy is genistein (Helferich, et al., 2008; M. Messina & Wu, 2009). Concentrations of genistein found in soy products are as high as 1.5 mg per gram of soy (Helferich, et al., 2008).

Because it is the most concentrated isoflavone found in soy, genistein has been a focus of a great deal of research. Genistein has been shown to have a greater binding affinity for beta estrogen receptors found in bone and the endothelial tissue of arteries and it, like other isoflavones, has preferential binding to beta estrogen receptors. However, genistein binds at 7.4% of estradiol’s binding capacity at beta estrogen receptors and binds at 0.017% of estradiol’s binding capacity at alpha estrogen receptors (Helferich, et al., 2008).

The potential estrogenic effects of isoflavones have been hypothesized to provide a variety of beneficial effects for both the menopausal and premenopausal woman. Because isoflavones are so similar in structure to estrogens they are able to activate estrogen receptors and therefore affect the transcription of messenger RNA. The isoflavones can act either as agonists or antagonists depending on the situation. For premenopausal women with significant levels of endogenous estrogen, isoflavones may act as antagonists by preventing them from binding, and by binding at a lower capacity compared to the endogenous estrogens. On the other hand, in postmenopausal women who have very low levels of endogenous estrogens, the isoflavones may act as agonists by binding to open estrogen receptors with some effect, albeit less than that of an endogenous estrogen. In this sense isoflavones could act as an alternative to estrogen therapy, and their selective binding makes them even more desirable by potentially decreasing the effect on the alpha estrogen receptors. Alpha estrogen receptors are found in endometrium, breast, ovarian stroma, and in hypothalamic tissue, whereas beta estrogen
receptors are found in the kidneys, brain, bone, heart, lungs, intestinal mucosa, prostate, and endothelial cells (Taylor, Levy, Elliott, & Burnett, 2009).

The beneficial effects of soy are not only related to its estrogenic-effects. Soy and isoflavones have cancer inhibitory properties including: inhibition of angiogenesis, cell proliferation and inflammation (Hall, et al., 2005; Lee, et al., 2009). Isoflavones provide anti-inflammatory effects by increasing the nitric oxide, which inhibits the activation of pro-inflammatory genes including: NFKB, cytokines, chemokines and cell adhesion molecules (Blum, 2003). Isoflavones positively affect the cardiovascular system by increasing the ratio of nitric oxide to endothelin and improving flow mediated endothelium dependent vasodilation (Atteritano, et al., 2007). Soy and isoflavones stimulate the production of sex hormone binding globulin (SHBG). SHBG has been associated with decreased concentrations of estradiol and lower breast cancer risk (Duncan, Merz-Demlow, Xu, Phipps, & Kurzer, 2000). Biological effects associated with reduced cancer risk that are attributed to soy include: the inhibition of tyrosine kinase activity, inhibition of topoisomerase II activity, arrest of cell cycle progression at the G2-M transition, and the fact that unlike exogenous estrogen, soy does not seem to show genotoxic and carcinogenic estrogen metabolites.

Not all of the potential effects of isoflavones are favorable. Though soy has been shown to have many antineoplastic effects it has also been suggested that some isoflavones may actually increase the risk of breast cancer. One study found that genistein, the most potent isoflavone in soy, stimulated the growth of estrogen dependent breast cancer tumors in vivo (Allred, Ju, Allred, Chang, & Helferich, 2001). Removal of genistein caused tumor regression. Yet, other studies have shown no promotion of breast tumor development by genistein (Gallo, Ferlini, Fabrizi, Prislei, & Scambia, 2006). It appears that the effect of genistein is dose-dependent; at
low concentrations it appears to have estrogenic effects and at high concentrations anti-
estrogenic effects (Helferich, et al., 2008). Another potentially negative effect of isoflavones,
genistein in particular, is that they may negate the inhibitory effect of breast cancer growth by
tamoxifen (Helferich, et al., 2008). Tamoxifen is a type of SERM used for treatment of
estrogen-sensitive breast cancer. It acts as an agonist at bone and uterine receptors and an
antagonist at breast estrogen receptors.

Vast amounts of epidemiological data support the beneficial effects of soy.
Epidemiologic data, mostly from Asian women, suggest diets high in soy are associated with
lower rates of breast cancer (Lee, et al., 2009) beneficial effects on the cardiovascular system
(Hall, et al., 2005), lower rates of fracture and less risk of osteoporosis (Kreijkamp-Kaspers, et
al., 2004; Marini, et al., 2007) and decreased rates of hot flash occurrence (Kang, et al., 2002).
Many of these potential benefits have been attributed to the estrogenic effects of isoflavones
found within soy.
Menopause

Menopause is a natural process women experience as they age. It is marked by the permanent cessation of menses and the loss of ovulation (Charles, et al., 2009). According to the Stages of Reproductive Aging Workshop (STRAW), menopause is recognized to have occurred after 12 months of amenorrhea with no obvious pathologic cause and reflects a near complete but natural diminution of ovarian hormone secretion. The menopause transition begins with variation in the length of the menstrual cycle caused by a rise in levels of monotrophic follicle stimulating hormone (FSH) and ends with the final menstrual period according to STRAW. For many women this transition may take years. Onset commonly occurs during the mid to late forties or early fifties and can occur naturally or be induced through medical intervention. With the average US life expectancy for a female extending into the eighth decade, women are now living close to half their lives after menopause (Soules, et al., 2001).

As the body changes so do hormone levels. The female reproductive hormones include estrogen, progesterone, FSH, and luteinizing hormone (LH). As women go through this transition these hormone levels fluctuate. During early menopause estrogen levels are generally normal but decrease as menopause progresses, while levels of FSH and LH begin to increase and continue to increase and plateau during menopause (Goldman & Ausiello, 2008). Since women no longer ovulate after menopause, progesterone and estradiol are no longer produced by the ovaries. However, other forms of estrogen are still produced in sites outside the ovaries, including estrone in the adipose tissue.

The decrease in estrogen coinciding with menopause has several detrimental effects for postmenopausal women. It has been associated with increased rates of bone remodeling, osteoclastic activity, and postmenopausal bone loss, potentially leading to
A mismatch between both reabsorption and formation occurs, causing first trabecular bone loss, followed by cortical thinning (Goldman & Ausiello, 2008). From the start of menopause bone loss averages 1% a year and by the time a woman turns sixty she will have lost approximately 25% of her total bone mass (Cleveland Clinic, 2009; Goldman & Ausiello, 2008). The World Health Organization defines osteoporosis as a condition in which bone mineral density (BMD) is less than -2.5 standard deviations below peak bone mass (Geneva: World Health Organization, 1998). Osteoporosis can lead to fragility fractures, which increase the morbidity and mortality of women. It is estimated 30% of white women in the US who are postmenopausal have osteoporosis (Sadat-Ali, et al., 2009).

Osteoporosis is not the only concern for women after menopause; cardiovascular concerns also become apparent. The cardiovascular problems occurring in association with menopause are also related to the decrease in estrogen production occurring after menopause. Coronary Artery Disease (CAD) and atherosclerosis are two of the cardiovascular risks associated with menopause. Estrogen helps maintain healthy levels of cholesterol in the blood, but when it decreases with menopause, cholesterol can increase to high levels and cause atherosclerosis, which may lead to CAD (Cleveland Clinic, 2009).
**Hormone Replacement Therapy**

Hormone Replacement Therapy (HRT) has been the long-standing treatment for menopausal symptoms including hot flashes and night sweats and has been approved by the FDA for such use (S. M. Penckofer, Hackbarth, & Schwertz, 2003). Decreased levels of estrogen play a role in causing many menopausal symptoms. Therefore, by providing an exogenous source of estrogen, commonly in the form of conjugated equine estrogen (CEE), women are able to decrease their menopausal symptoms.

However, side effects were found with the use of synthetic estrogen-only preparations. The side effect that was of greatest concern was increased endometrial hyperplasia in women with an intact uterus. The use of estrogen-only preparations resulted in close to double the number of endometrial cancers found per thousand users within a five year period (9 total, 4 additional) when compared to non-users rate of approximately five per thousand, per five year period (Beral & Million Women Study, 2003). To offset this side effect, a form of progestin, was often added to counteract the estrogen. It decreased the hyperplasia, and the risk of endometrial cancer. Its addition resulted in little to no change in incidence of endometrial cancer compared to women without any use of hormonal treatments. The estrogens’ effect on menopausal symptoms is not changed with the addition of progestin, so women still gain the benefit of decreased menopausal symptoms.

In the 1980s and 1990s it was suggested that since HRT decreased menopausal symptoms in women, it could potentially benefit other menopausal related issues.. Two of the main detrimental effects associated with menopause are increased rates of osteoporosis and cardiovascular disease (S. M. Penckofer, et al., 2003). Several studies looked into the use of HRT for these conditions.
Cardiovascular Disease

A 40-50% reduction of risk of cardiovascular disease was suggested with use of HRT by several epidemiological studies (S. M. Penckofer, et al., 2003). Although several significant limitations were found for the studies, they still supported the potential use of estrogen as a preventative treatment for cardiovascular disease in menopausal women. Some of the suggested benefits of HRT were alteration in the activation of blood monocytes, antioxidant and antiplatelet activity, positive effects on cardiac function and vascular resistance, decreased levels of endothelin-1, cell adhesion molecules, and calcium in coronary plaques (Kok, Kreijkamp-Kaspers, Grobbee, Lampe, & van der Schouw, 2005; S. Penckofer & Schwertz, 2001; Wilcox, Hatch, Gentzshein, Stanczyk, & Lobo, 1997). These beneficial effects, as well as evidence that HRT improved lipid profiles supported the use of HRT as a way to decrease the progression of atherosclerosis, providing cardioprotection.

The Heart Estrogen Replacement Study (HERS I) published in 1998, was a randomized controlled trial that followed 2,763 postmenopausal women with a history of CHD for an average of 4.1 years, showed that there was an increase in the risk of cardiac events in women taking 0.625 mg/day CEE) plus 2.5 mg medroxyprogesterone acetate, versus placebo. It also noted that within the first year, particularly within the first four months of treatment, women were more likely to experience cardiac events. Although, the population studied was older (with a mean age of 67) and had history of CHD (Grady, et al., 2000). HERS II prolonged the study by adding almost three years onto the original five year HERS I. They followed the original participants to see if continued long-term treatment reduced the risk of cardiac events. The results did not support any decreased risk. In fact, the trial showed that there was no beneficial
effect of hormone therapy in women with established coronary heart disease (CHD) (Grady, et al., 2002).

The Women’s Health Initiative (Rossouw, et al., 2002) was the next major study to provide information on HRT. It was a large, randomized controlled study involving 16,608 postmenopausal women aged 50-79 with an intact uterus between 1993 and 1998. Participants with a uterus received either 0.625 mg/day of CEE plus 2.5 mg/day of medroxyprogesterone acetate or placebo. Women without a uterus received with 0.625 mg/day of CEE or placebo. Medroxyprogesterone acetate (MPA) is a type of synthetic progesterone and CEE is a synthetic form of estrogen. The study assessed the incidence of CHD in women using HRT and the overall risks and benefits of the use of HRT on postmenopausal women’s health. The results were surprising; just four years into the projected eight-plus-year study adverse effects on cardiovascular disease were seen with the use of this form of HRT. This finding was not significant enough to stop the trial, but the statistically significant increased risk of breast cancer and overall harm was. The trial was stopped in May of 2002 (Rossouw, et al., 2002).

Analysis of the four year trial showed increased risk of several cardiovascular factors with use of CEE-MPA HRT. Events requiring hospitalization, including cardiovascular disease, were increased by 22% in women on HRT. Seven more women per 10,000 person years suffered from some form of CHD when assigned to the HRT group. The comparison was 30 incidents of CHD for placebo versus 37 incidents of CHD for CEE and MPA HRT groups. This accounts to an increased relative risk somewhere between 2% and 63% for CHD among HRT users. Most of these were cases of non fatal myocardial infarction (Rossouw, et al., 2002).

Stroke rates were also higher among HRT users, with a 41% increase compared to placebo. The increased risk of stroke was consistent with the findings from the HERS, which
showed a 23% increase of stroke in the HRT group, which did not reach statistical significance (Rossouw, et al., 2002).

The most statistically significant cardiovascular difference between the HRT group and placebo was the increased risk of thromboembolism including both increased risk of deep venous thrombosis (DVT) and pulmonary embolism (PE). Women receiving HRT were more than twice as likely to develop some form of thromboemoblism comparatively. The relative risk of thromboembolism was 111% for HRT users. However there was no significant difference between groups in regards to overall death (Rossouw, et al., 2002).

The results from the WHI as well as HERS I and II showed that HRT was not only an ineffective preventative treatment for cardiovascular illness; it actually had negative effects on women’s cardiovascular health. According to the American Heart Association, HRT should not be used for primary or secondary prevention of cardiovascular disease (CVD) (Mosca, et al., 2001). The only approved use for HRT is for menopausal vasomotor issues and it is recommended that the lowest dose for treatment of symptoms be used for the shortest period of time possible.

However, estrogen alone does have some positive cardiovascular effects including: decreasing the development of atherosclerosis, facilitating vasodilatation, and decreasing inflammatory response. The previous studies demonstrated how estrogens use in the form of CCE-MPA preparation was too much of a health risk for it to be a viable option for prevention of cardiovascular disease in postmenopausal women. Alone, estrogen is associated with increased risk of endometrial cancer and therefore is not a viable option for women with a uterus as an individual treatment. The potential to manipulate an estrogen like therapy to provide the
beneficial cardiovascular and bone effect of estrogen without the increased rates of endometrial cancers and detrimental cardiovascular and breast effects would be ideal.

**Breast Cancer**

Though hormone therapy had many effects on the cardiovascular system, it was its adverse effects on the breast that led to the premature discontinuation of the WHI. Breast cancer was designated as the primary adverse outcome for the initiative. The global index for breast cancer reached a rate supportive of finding overall harm, and the study was discontinued. There was a 26% increase in the rate of invasive breast cancer for the CEE-MPA group, with 8 more cases per 10,000 person-years. Use for greater than 5 years resulted in a 53% increase in risk. These results were found to be highly significant and crossed racial, ethnic, and age groups (Rossouw, et al., 2002).

The Million Women Study reinforced what the WHI had found, that women on hormonal treatment were at increased risk of breast cancer. It involved 1,084,110 UK women aged 50-64 and compared the different types of hormone therapy with results showing that the CEE-MPA combinations similar to the ones used in the WHI were associated with the highest increase in risk of invasive breast cancer. Regardless of type of HRT, the longer women used the therapy, the greater their risk of developing breast cancer. Ten or more years of hormone therapy was associated with a relative risk of 1.37 (95% confidence Interval (CI) 1.22-1.54) for those using CEE-only treatments, while those using estrogen-progestin treatments had a relative risk of 2.31 (95% CI 2.08-2.56) of developing invasive breast cancer (Beral & Million Women Study, 2003). Women receiving HRT also had increased rates of *in situ* breast cancer particularly in the CEE-MPA group, with a hazard ratio of 1.18 (P=0.09). Forty-seven cases of *in situ* breast cancer were found in the CEE-MPA group compared with only 37 cases found with placebo. Interestingly,
previous users of HRT were not at an increased risk of breast cancer comparatively (Chlebowski, et al., 2003).

Women receiving the CEE-MPA prep also had increased rates of abnormal mammograms, with an absolute increase of approximately 4% per year (Chlebowski, et al., 2003). After only one year, a total of 31% of the women using the CEE-MPA preps had at least one abnormal mammogram. A substantial increase in mammographic density, which is a predictor for breast cancer, was one of the abnormalities found on mammogram (Rossouw, et al., 2002).

HRT also decreased mammographic sensitivity, thus making it more difficult to detect the breast cancer on screenings (Beral & Million Women Study, 2003). When found, tumors were larger in size and more advanced when compared to placebo (Chlebowski, et al., 2003). Because more advanced and invasive tumors have a poorer prognosis, it is not surprising that current users of HRT also had significantly increased mortality rates due to breast cancer, when compared to non-users. Not only were current users more likely to develop breast cancer, the Million Women Study showed that they were also more likely to die from it. Current users had a relative risk of death from breast cancer of 1.22 (CI 1.05-1.41) compared to 1.0 ( CI 0.88-1.14) for never users (Beral & Million Women Study, 2003).

Throughout the Million Women Study CEE-only preparations had decreased risk of breast cancer when compared to the CEE-MPA preparations. When used for less than ten years CEE-only preparations had relatively low increased risk of breast cancer (Beral & Million Women Study, 2003). In the WHI CEE-only trial women were 18% less likely to develop invasive breast cancer compared to placebo when followed for an average of over seven years. Even more impressive was that adherent subjects’ risk of breast cancer dropped by one-third, and
their incidence of localized breast and ductal carcinoma dropped by approximately 30% each. Estrogen use in breast cancer survivors also is of minimal risk, with low rates of recurrence, and mortality due to breast cancer (M. J. Messina & Wood, 2008).

The final determination was more harmful than beneficial outcomes with the use of CEE-MPA HRT in comparison to the placebo group. Though there were a significant number of harmful outcomes with the use of HRT, there were also several beneficial results, however these results, were overshadowed by the gross negative effects associated with breast cancer and cardiovascular disease. Two beneficial effects of HRT found by the WHI were decreased rates of colorectal cancer, and hip fractures.

**Osteoporosis**

Hip fracture was designated as secondary outcome for study during the WHI due to the increased prevalence of osteoporosis associated with postmenopausal women. Estrogen plays a complex role in regards to the development of bones. It is known to help maintain bone mineral density both alone and with progestin. Calcium absorption is increased with the use of HRT to rates similar to perimenopausal women (Spence, et al., 2005). Therefore, it was theorized that replacing the decreased levels of estrogen associated with menopause would potentially decrease the bone loss that goes along with it. Hip and vertebral fracture rates were both reduced by one-third with the use of HRT compared to placebo. The decrease of other fractures associated with osteoporosis and the overall decrease in total number of fractures were statistically significant (Rossouw, et al., 2002).

HRT is an option for treatment of osteoporosis since it is effective in reducing postmenopausal bone loss. However, there are a variety of other, options available. Therapies including the use of bisphosphonates, SERMs, and calcitonin are all viable options from the
treatment of osteoporosis. The substantial risks associated with HRT must be evaluated when HRT is considered as an option for prevention of osteoporosis.

HRT is still an approved treatment for menopausal symptoms but it is recommended that the lowest dose of hormones be used for the shortest period of time possible. Age and timing, in regards to menopause, play important roles on the effects, and level of risk associated with its use (S. M. Penckofer, et al., 2003). At this point HRT is not recommended as primary or secondary route of prevention of cardiovascular disease (Rossouw, et al., 2002). HRT is not an effective treatment for cardiovascular disease or breast cancer and its effect on osteoporosis comes with increased risk of other illness. An alternative option with greater effects on the focused area of treatment and less negative effects is needed.
Isoflavone Safety

Soy has been a major component of Asian diets for centuries. Its consumption has generally been assumed to be safe, and potentially even beneficial. However, the recent interest in the use of soy, and the isoflavones found within it, has raised concerns about the safety of these compounds. The estrogenic activity of isoflavones may produce some negative effects especially for women with estrogen-sensitive breast cancer, so it is important to analyze the safety of these natural compounds before recommendations for use of soy and soy isoflavones can be determined.

Epidemiological evidence supports the safety of consumption of soy isoflavones at rates similar to those found within Asian diets (Trock, Hilakivi-Clarke, & Clarke, 2006). However, side effects are a concern for any potential treatment, so it is important to determine the safety profile and side effects associated with the use of soy isoflavones at various dosages. Clinical studies have supported a positive safety profile for soy and soy isoflavones at a variety of dosages, ages, and lengths of consumption, with the most common side effect being mild gastrointestinal effects (Atteritano, et al., 2007; Gleason, et al., 2009; Hooper, et al., 2009; MacGregor, Canney, Patterson, McDonald, & Paul, 2005). Results varied, but in general, epidemiological and clinical studies agree that soy is relatively safe, and its consumption at healthy levels is acceptable for most women. One systematic review of 47 studies involving isoflavones found the only significant side effect of soy isoflavones in comparison to placebo to be gastrointestinal (GI) side effects. Gastrointestinal side effects in pre and postmenopausal women combined were found to have a relative risk (RR) of 1.8, (95% Confidence Interval (CI) 1.3 to 2.6) out of eight studies. There was no significant difference in the dropout rate from the study due to the severity of the side effects (Hooper, et al., 2009).
Gastrointestinal side effects were also the most common side effect of isoflavone use noted in clinical trials. These gastrointestinal side effects included: abdominal or epigastric pain or discomfort, nausea, vomiting, loss of appetite, dyspepsia and constipation (Atteritano, et al., 2007; Gleason, et al., 2009; MacGregor, et al., 2005; Pop, et al., 2008). Adverse effects were reported by 19% of postmenopausal women receiving 54 mg/d of genistein over the course of 2 years, all associated with gastrointestinal discomfort, requiring them to discontinue therapy. Comparatively, only 8% of the placebo recipients in the same study of 389 postmenopausal women discontinued therapy due to adverse effects (Atteritano, et al., 2007).

As mentioned previously with HRT, exogenous forms of estrogen combined with progestin increased the risk of cardiovascular problems in postmenopausal women. Soy has been proposed to have estrogen like qualities and to potentially be able to act as a SERM so it is important to assess its effect on the cardiovascular system in comparison to hormonal therapy. Postmenopausal women in a two year trial using genistein reported similar levels of LDL, HDL, cholesterol, lipoprotein A and triglycerides in comparison to placebo. These are all markers predictive of cardiac risk. Therefore, in regards to the previous risk factors, genistein use was not associated with increased risk of cardiovascular injury compared to placebo (Atteritano, et al., 2007).

Another potential negative side effect of isoflavones acting as SERMs, is a potential to act on endometrial tissue, another site for estrogen receptors. Out of all of the clinical trials reporting side effects only one patient in one study reported vaginal bleeding as an adverse effect (MacGregor, et al., 2005), and two studies which measured endometrial thickness as a potential adverse effect of isoflavone supplementation found no significant changes in thickness in
comparison to placebo over two and three years respectively (Atteritano, et al., 2007; Marini, et al., 2008).

Because of estrogenic effects associated with soy products, it is important to assess the safety of soy in regards to the change in estrogen associated hormones. The effect of soy on such hormones, if significant enough, could have negative long term effects on either pre or postmenopausal women. In a meta-analysis of 47 studies including eleven with premenopausal women, thirty-five with postmenopausal women and one with perimenopausal women, soy, or isoflavone consumption, had no significant effect on estradiol, estrone or SHBG and in postmenopausal women no significant effect on FSH or LH either. FSH and LH were significantly decreased in the soy isoflavone group of premenopausal women, and estradiol was increased in the postmenopausal women taking soy isoflavones (Hooper, et al., 2009). However, the changes were modest, and their implications on women’s health are unknown. These small changes and lack of change of FSH, LH, and SHBG do not support a strong estrogenic effect for isoflavones. These findings were supported by several other studies, which found no significant changes in levels of estradiol, FSH, LH and SHBG levels (Gleason, et al., 2009; Pop, et al., 2008).

The majority of the studies focused on pre and postmenopausal women so it is important to support the safety of soy in populations outside the standard range; men and women of increasing age, as well as younger women and teens, need to be included to evaluate the safety of soy consumption throughout life. A randomized controlled trial, focusing on the safety of soy isoflavone supplements in men and women aged 62 to 89 years old, found them to be well tolerated in older adults. Though the study was small, including only thirty subjects, it was six months long and was randomized, with patients receiving either 100 mg/day of isoflavones or
placebo for six months. Adherence was also very good; with rates close to 98% for both placebo and isoflavone groups. Few adverse symptoms were reported in total, and there was no significant difference between the groups in number or type of symptoms reported. Vital signs, and basic laboratory tests were also assessed, without any significant difference between the two groups. Soy isoflavones had a side effect profile comparable to that of placebo (Gleason, et al., 2009).

Isoflavones’ general safety profile was also assessed using several blood parameters. No significant change in pancreatic enzymes (lipase, amylase), phosphate, or liver enzymes (AST, ALT, GGT) were found following consumption of 54 mg/day of genistein for three years or 100 mg/day of isoflavones (85% diadzein and genistein) for six months (Gleason, et al., 2009; Marini, et al., 2008).

The most supportive results for the safety of soy isoflavones in the diet of women would be the results from a phase one clinical trial which found isoflavones to be safe and well tolerated among postmenopausal women at doses as high as 900 mg/day (Pop, et al., 2008). This greatly exceeds the average consumption associated with Asian diets.

**Breast Safety**

One of the areas of most concern in regards to the use of soy isoflavones is the breast. As a potential substitution for HRT, and with qualities that suggest soy to have estrogen-like effects, it is important to rule out any increased risk of breast cancer that could potentially be associated with the use of isoflavones. Also, determining the safety of isoflavone use by survivors of breast cancer, particularly those with estrogen-sensitive breast cancer, is of importance.

Epidemiological evidence supports the safety of isoflavones even in survivors of breast cancer. Asian women who are more likely to consume diets high in soy, are less likely than their
Western counterparts to develop breast cancer, which leads to the belief that soy, rather than causing increased risk, may actually be protective in regards to the development of breast cancer. The estimated average intake of isoflavones by Americans is approximately 1-3 mg/day. In comparison, the estimated Asian intake is much higher ranging from 25-40 mg/day (Duncan, et al., 2000).

The beneficial effects of soy at levels close to the average consumption by Asian women are supported by a recent meta-analysis. The meta-analysis was composed of twenty-eight studies focusing on soy and breast cancer risk, fourteen were in Western populations, and fourteen were in Asian populations. The Western studies had relatively low intake of soy isoflavones. Eleven studies involving Western diets found no association between isoflavone intake and breast cancer risk although isoflavone intake was much lower in this group, with the highest intake only 0.8 mg/day. In comparison the Asian studies had much higher average intakes of soy. Meta-analysis of eight of the fourteen Asian studies found decreased risk of breast cancer with increasing isoflavone intake. Compared to the lowest level of intake (<5 mg/day isoflavones) which would encompass the Western average, intake of approximately 10 mg of isoflavones daily was associated with a 12% reduction in breast cancer risk. The highest group of soy consumers, with intake of 20 mg or more a day had a 29% reduction in breast cancer comparatively (Wu, Yu, Tseng, & Pike, 2008).

Another meta-analysis suggested a similar though smaller inverse association between soy intake and breast cancer risk. This analysis included eighteen epidemiological studies (12 case control and 6 cohort or nested case control) published between 1978-2004. It found that high soy intake was modestly associated with reduced breast cancer risk (OR=0.86, 95% CI =0.71-1.12), and noted that the inverse association between soy exposure and breast cancer risk
was somewhat stronger in premenopausal women (OR = 0.70, 95% CI= 0.58-0.85) than in postmenopausal women (OR=0.77, 95% CI = 0.60-0.98) (Trock, et al., 2006).

Dosing and length of consumption also appear to play important roles on the effects of isoflavones. The Singapore Chinese Health Study, a cohort study involving 35,303 Chinese women aged 45-74 years old, also found an inverse association between intake of isoflavones and risk of breast cancer. An 18% risk reduction was found with intake of 10.6 mg 1000Kcal\(^{-1}\) or more of soy isoflavones daily. This dose is similar to the dose used by Wu, of 10 mg/day of isoflavones and the decreased risk is similar as well, Wu had a 12% decrease. The reduction in the Singapore study was significant for postmenopausal women and was found regardless of estrogen and progesterone receptor status. Premenopausal women did not have the same statistically significant reduction of risk. However, only approximately one-fourth of participants were under fifty years old upon enrollment. Suggesting even more beneficial long term effects of consumption of soy, was that the protective effect of increased soy intake was clearly statistically significant among women with greater than ten years of follow up (RR=0.48, 95% CI = 0.29-0.78) Those with less than ten years follow up had a significantly smaller risk reduction (0.88, 95% CI= 0.74-1.05). Also of importance was the lack of protection noted in the Asian groups consuming the lowest levels of soy isoflavones. This supports the epidemiological association that soy consumption and not just genetics is responsible for the decreased rates of breast cancer among Asians (Wu, Koh, Wang, Lee, & Yu, 2008).

A recent nested case control study from the Japan Public Health Center used plasma concentrations, a potentially more sensitive predictor of soy isoflavone effects, to determine the association between isoflavones and breast cancer. This cohort included 24,226 Japanese women aged 40-69 years old who responded to a baseline questionnaire and provided plasma
samples and were followed for an average of 10.6 years. They found that relatively high dose isoflavone exposure that was achievable from dietary intake alone was associated with decreased risk of breast cancer. They observed an approximately 65% reduction in breast cancer risk in the highest plasma genistein quartile group, although the other quartiles experienced no decrease. Their adjusted relative risk for breast cancer for the highest compared with the lowest quartile of plasma genistein concentrations was 0.34 (95% CI 0.16-0.74; P 0.02). Dietary genistein intake was not statistically significant although it also appeared to be protective to a lesser extent (RR 0.58, 95% CI 0.29-1.18; P 0.21) (Iwasaki, et al., 2008).

Two other studies were not able to conclude a decreased risk of breast cancer with increased consumption of soy isoflavones. Instead, they both found no association between isoflavone intake and breast cancer risk, positive or negative. The first study was a prospective population based cohort study among Swedish pre and postmenopausal women. In included 49,261 women aged 30-49 years old, and followed them for thirteen years. It found that the intake of phytoestrogens, including isoflavones, did not differ substantially between women who did, and did not develop breast cancer. Estrogen-progesterone receptor status did not change the results and risk estimates were similar for breast cancer occurring before or after fifty years of age. However, the isoflavone intake in this study was low, measuring less that 0.1 mg/day, since Swedish intake of soy is generally low throughout the population (Hedelin, et al., 2008).

The European Prospective Investigation into Cancer and Nutrition (EPIC) was the second study to find no association between isoflavone intake and breast cancer risk. It included a cohort of 37,643 British women twenty years or older, among whom there was considerable dietary heterogeneity because of the deliberate oversampling of individuals with meat free diets. Thirty-one percent of the women were vegetarians. The women were followed for 7.4 years
during which 585 cases of breast cancer occurred. Isoflavone intake was significantly higher among vegetarians in comparison to non-vegetarians. Vegetarians consumed an average of 10.2 mg/day of isoflavones, in comparison to only 2.9 mg/day consumed by non-vegetarians. The vegetarian group was also younger, with 76% premenopausal. The study is unique in that it is the only large scale, Western study, not involving Asians, in which isoflavone consumption was comparable to that of Asians. Even though close to 1/3 of the cohort (27%) was consuming 10 mg or more of isoflavones daily, there was no evidence for a relationship of risk for breast cancer with isoflavone intake (Travis, et al., 2008). However, they failed to find any increased risk of breast cancer with increased levels of consumption of soy, which supports its safety in regards to breast cancer risk.

Also of concern is the safety of isoflavones for use by survivors of breast cancer and those at increased risk of developing breast cancer. The Life After Cancer Epidemiological Study (LACE) followed 1,954 mostly Caucasian women diagnosed with breast cancer between 1997-2000 for over six years. It found a non-significant decreased risk of breast cancer recurrence with increased consumption of soy isoflavones, diadzein and glycetin. Women with the highest rate of consumption of diadzein and genistein had an approximately 50% reduction in breast cancer recurrence although it was not significant for genistein (HR 0.48, 95% CI 0.19-1.22) and diadzein (HR 0.48, 95% CI 0.19-1.21) (Guha, et al., 2009).

It has also been proposed that because of potential estrogenic effects, isoflavones may increase growth and recurrence of estrogen-sensitive breast cancers because of binding to the estrogen receptors. The LACE study analyzed the effect of increasing levels of isoflavone intake among tumors that were estrogen receptor positive (ER+) and negative (ER-) and progesterone receptor positive (PR+) negative (PR-). Unlike the Singapore Chinese Health Study, the LACE
study found increasing isoflavone intake to decrease the risk of recurrence of cancer among
tumors that were ER + and PR+ but not ER- and PR- in breast cancer survivors. One strength of
this study was that it was comprised of mostly Caucasian females, unlike the previous meta-
analyses, which consisted mostly of Asian females. However, this strength was also a weakness
because Caucasian females had relatively low consumption of soy foods, with the highest intake
group consuming ≥ 9.6 mg/day (Guha, et al., 2009).

The Shanghai Breast Cancer Survival Study supported the findings of the LACE study
and confirmed the safety of soy isoflavones for use in women with breast cancer. It found that
soy consumption was significantly associated with decreased risk of mortality and recurrence of
cancer among 5,042 female breast cancer patients in China aged 20-75 years old. Like Wu, they
also noted a linear dose response pattern; this time with the key dosage being 11 g/day of soy (40
mg of isoflavones), in comparison to Wu’s 10 mg/day of isoflavones (Shu, et al., 2009; Wu,
Koh, et al., 2008). At doses higher than 11 g/day of soy, no increased benefits on mortality or
recurrence were noted (Shu, et al., 2009). These findings were consistent among menopausal
status, cancer stage (early –late), and estrogen and progesterone receptor status.

Overwhelmingly positive epidemiological studies, supporting either no change or a
decreased risk of breast cancer in association with the consumption of soy and soy by-products,
support the safety of this food for both pre and postmenopausal women. Several of these studies
have noted positive associations between the use of soy and decreased rates of breast cancer
recurrence in women with or without a history of breast cancer, making soy appear to be safe for
all women including those with breast cancer. In fact a recent review of the safety of isoflavones
in regards to breast cancer risk noted that there was little clinical evidence to suggest that
isoflavones will increase breast cancer risk in healthy women or worsen the prognosis of breast cancer patients (M. J. Messina & Wood, 2008).

Fewer clinical trials have assessed the safety of soy isoflavones but several had positive findings. A review of the safety of genistein noted that several clinical studies using postmenopausal women support the breast and uterine safety of purified naturally derived genistein administered for as long as three years. It suggested that genistein is safe for use by perimenopausal and postmenopausal women with no history of breast or reproductive organ cancers. This review supported the safety of genistein because of its ability to cause cancer cell apoptosis in vitro and protect against the development of carcinomas in animal models. Genistein does not cause the development of new estrogen-dependent breast or reproductive tissue cancers (Taylor, et al., 2009).

Clinical studies using human data suggest that soy isoflavones are safe. Three clinical studies have analyzed mammographic densities before and after isoflavone treatment and results showed changes similar to those found in placebo for all groups. (Table) Increased mammographic density is used as a marker for increased risk of breast cancer. Isoflavone daily dosage was varied, and ranged from 54 mg/day to greater than 120 mg/day and the studies ranged in length from one to three years (Marini, et al., 2008; Maskarinec, et al., 2009; Verheus, et al., 2008).

One randomized double blind placebo controlled trial involving 389 postmenopausal women receiving 54mg of genistein aglycone daily for three years, found genistein to exhibit a promising safety profile. This study used mammographic breast density to determine rates of breast cancer, and included BRCA1 and BRCA2 levels. No significant differences in
mammogram density were found between the genistein group and placebo over the three year span. BRCA1 and BRCA2 levels were different between groups but no significant change was observed over time within the genistein group, whereas the placebo group experienced a reduction in both. BRCA1 and 2 were used as identifiers of increased risk of breast cancer. BRCA1 inhibits estradiol up-regulation of extracellular signal related kinase, which is specifically implicated in breast cancer cell proliferation. BRCA2 helps to maintain genomic integrity. The conserved levels of BRCA1 and 2 suggest that genistein may help to maintain apoptotic potential and preserve DNA repair capacity in breast tissue (Marini, et al., 2008).

**Tamoxifen –Soy Safety**

An additional area of concern for safety is for breast cancer survivors using anti-estrogenic therapy such as tamoxifen. Tamoxifen is a SERM that is used in the treatment of ER+ breast cancer. It competitively inhibits the estrogen receptor, and has been shown to induce apoptosis and G1 cell cycle arrest in human breast tissue (J. L. Jones, Daley, Enderson, Zhou, & Karlstad, 2002). Isoflavones have been reported to cause breast cell stimulation and it has been proposed that isoflavones may interfere with the function of tamoxifen, by inhibiting some of tamoxifen’s beneficial effects on the breast for breast cancer survivors. Because more than 60% of breast tumors are ER+, and tamoxifen is a first line treatment for these ER + tumors, it is important to assess the interaction between these two chemicals before safety guidelines for use of isoflavones can be evaluated (J. L. Jones, et al., 2002).

*In vitro* and animal studies have raised questions about the safety of isoflavones when used in conjunction with tamoxifen. In some studies the inhibitory effects of tamoxifen on the growth of estrogen-dependent tumors were negated by the presence of isoflavones such as genistein. One study found dietary genistein to abrogate the inhibitory effect of tamoxifen on
breast cancer cell (MCF-7) tumor growth (Helferich, et al., 2008). Another study, using genistein on human breast cancer cells, found it to inhibit the effects of tamoxifen on cell proliferation and cell cycle arrest in T47D cells. The study showed that tamoxifen alone caused a small but significant decrease in breast cancer cell growth causing an 8% reduction in proliferation. When genistein alone was added to cells, no decrease in proliferation was seen. When the combination of genistein and tamoxifen were added to T47D cells, only a 3.3% reduction in proliferation was seen. Genistein in combination with tamoxifen caused a 5% smaller decrease in cell proliferation in comparison to tamoxifen alone. In association with these findings, it appears that genistein may interfere with the effects of tamoxifen under certain conditions, so it is best for women taking tamoxifen to be cautioned about the use of soy products and their potential effects on the efficacy of tamoxifen (J. L. Jones, et al., 2002).

In contrast, two other in vitro studies found genistein and tamoxifen to synergistically inhibit breast cancer cells. The first study found the combination of tamoxifen and genistein to synergistically induce apoptosis of a type of human breast cancer (BT-474) cells. Genistein alone at doses ranging from 3.125-25µm showed both time dependent and dose dependent effects on growth inhibition of BT-474 cells. Tamoxifen also inhibited these cells growth. In combination, tamoxifen and genistein caused a significant growth inhibition that was greater than either treatment alone. Cell growth was reduced by 96% with the combination of 5µM of tamoxifen and 25µM of genistein (Mai, Blackburn, & Zhou, 2007).

The second study had results similar to the first. It too found genistein to inhibit the growth of malignant epithelial breast cancer cells, and the addition of tamoxifen had synergistic inhibitory effects as well. Genistein was shown to have a significant, dose-dependent effect on dysplastic (MCF-10A, MCF- ANeoT, MCF-T63B) and malignant cells (MCF-&., MDA-231,
Although, it’s inhibitory effects were greater on dysplastic cells (Tanos, Brzezinski, Drize, Strauss, & Peretz, 2002).

Between the two studies, genistein was shown to have significant inhibitory effects on seven different types of malignant or dysplastic breast cell lines. In the MCF-10A cell line, addition of 10 µg/ml of genistein reduced dysplastic cell proliferation from 106 to 61% and when tamoxifen was added, the growth rate was reduced from 93 to 5%. Similar effects were seen throughout other cell lines. Importantly these synergistic effects were apparent in all types of cells, and were independent of estrogen receptor expression (Tanos, et al., 2002).

Lastly several human studies have taken into account the effects of soy isoflavones and tamoxifen use. None of these studies found soy or soy isoflavones to negatively affect tamoxifen or breast cancer rates. A cross sectional study of 380 Asian American breast cancer survivors who used tamoxifen, found no evidence that soy intake adversely affected levels of tamoxifen or its metabolites. Circulating levels of tamoxifen and its metabolites were unrelated to intake of soy measured by self reported isoflavone intake, serum concentration levels of isoflavones, and soy intake near time of blood draw. This study found soy isoflavone intake to neither positively nor negatively influence circulating levels of tamoxifen or its metabolites (Wu, et al., 2007).

The LACE study evaluated the association between soy isoflavone intake after diagnosis of breast cancer, with cancer recurrence. A 60% reduced risk of cancer recurrence was associated with postmenopausal women treated with tamoxifen, who were receiving the highest, compared to lowest, intake of diadzein (>1,453 vs. <7.7 µg/day: HR 0.48, 95% CI 0.21-0.79). Women who used tamoxifen had a significantly decreased risk of breast cancer recurrence with increased intake of glycetin and smaller non-significant relationship for intakes of daidzein and
genistein. Among women treated with tamoxifen, consumption of soy products after a breast
cancer diagnosis may be associated with a reduced risk of recurrence (Guha, et al., 2009).

Finally the Shanghai Breast Cancer Survival Study found similar results to the LACE
trial when analyzing isoflavone intake and tamoxifen use. It found no difference in the risk of
relapse of breast cancer among women whose soy food intake was highest, regardless of
tamoxifen use. Participants in the highest quartile of soy intake, who did not take tamoxifen, had
an HR of 0.65 (95% CI 0.36-1.17), while those that did take tamoxifen in the highest quartile had
an HR of 0.66% (95% CI 0.58-1.51). Soy intake was associated with improved survival,
regardless of tamoxifen use, while tamoxifen use was related to improved survival only among
women who had low or moderate levels of soy intake. Tamoxifen had no beneficial effect on
those in the highest quartile of soy intake were (Shu, et al., 2009).

Though conflicting results have been found, which question the effects of isoflavones on
breast cancer incidence; isoflavones do not appear to negate the effects of tamoxifen. Clinical
and epidemiological evidence supports of the safety of this combination. In fact, the American
Cancer Society (ACS) in 2006 recommended that up to three servings of traditional soy foods
per day were safe for breast cancer patients to consume. However, the ACS did not support the
use of more concentrated sources of isoflavones in patients with breast cancer (Doyle, et al.,
2006). No randomized controlled trials have evaluated the effect of soy or soy isoflavones on
breast cancer recurrence so far. Therefore, further research including randomized controlled
trials, is still needed to definitively validate the safety of isoflavones in different populations and
varieties of doses.
**Soy Isoflavone Efficacy**

How efficacious soy isoflavones are in preventing breast cancer and osteoporosis and cardiovascular illness is still being evaluated. While they have been proposed to have positive effects on bone mineralization and cardiovascular markers, as well as having preventative effects on breast cancer, there is still great debate about each of these potential uses. Research on the effect of soy isoflavones on bone has varied in their results pertaining to these potential effects.

**Treatment and Prevention of Osteoporosis**

Several studies have found soy isoflavones to produce beneficial effects on bone in primarily postmenopausal women with osteoporosis. Other studies have contradicted these results in populations of healthy postmenopausal women. Epidemiological data supports the beneficial effects of soy. Asian countries, with higher rates of consumption of soy, have lower rates of fractures associated with osteoporosis as compared to their Western counterparts (Somekawa, Chiguchi, Ishibashi, & Aso, 2001). Epidemiological studies also found that women who ingest higher amounts of phytoestrogens, particularly soy isoflavones, have less risk for osteoporosis (Marini, et al., 2007).

One study involving 478 postmenopausal Japanese women found high consumption of soy products (≥65 mg/day) to be associated with increased bone mass. Early postmenopausal women showed significantly different BMD between four groups of soy intake (Low < 35 mg/day-High ≥65 mg/day). The groups with intake >50 mg/day had higher BMD than the lowest intake group (<35 mg/day P<0.001). Late postmenopausal women also had significantly higher bone mineral densities with increasing rates of soy consumption (Somekawa, et al., 2001).

In general, clinical trials have shown soy isoflavones to provide positive effects on bone loss in osteopenic postmenopausal women (Marini, et al., 2008; Marini, et al., 2007). However,
healthy postmenopausal women did not have as conclusive results, and the one study that incorporated premenopausal women had positive results that were so small they were considered to be irrelevant clinically (Wangen, et al., 2000). A two year randomized controlled trial involving 389 osteopenic postmenopausal women between the age of 49-69 with BMD less than 0.795g/cm² found that 54mg a day of genistein had positive effects on BMD. Genistein also had favorable effects on markers of bone metabolism. It decreased levels of bone resorption markers and increased levels of markers of new bone formation which produced a net gain of bone mass after the first and second year of therapy. Genistein produced a significant increase in lumbar spine BMD (change, 0.049 g/cm², 95% CI, 0.035 - 0.059) with a difference of 0.10 g/cm² (CI, 0.08 - 0.12; P<0.001) compared to placebo. It also produced an increase in femoral neck BMD (change, 0.03510g/cm², 95% CI 0.025-0.042) with a difference of 0.062g/cm² (95% CI 0.049-0.073; P< 0.001) compared to placebo (Marini, et al., 2007). A follow up study extended the original two year study to three years and the positive effects of genistein were continued. The follow up included 138 of the original 389 osteopenic patients and found genistein to significantly increase BMD at the femoral neck and lumbar spine, compared to placebo through the third year. Importantly, genistein continued to have positive effects on markers of bone metabolism. It continued to decrease levels of bone resorption markers (PYR, CTX and sRANKL) and increased new bone formation markers (B-ALP, IGF-I and OPG) through to the third year (Marini, et al., 2007). In agreement with the previous studies, Atteritano et al. found an increase in spine and hip BMD with genistein compared to spine and hip BMD loss with placebo when studying young postmenopausal women with osteopenia (Atteritano, et al., 2009).

Studies involving healthy postmenopausal women have been more mixed. Several randomized controlled trials evaluated the effects of soy isoflavones or genistein on bone health
in early postmenopausal women (Brink, et al., 2008; Morabito, et al., 2002). An improvement in BMD after daily consumption of 54mg/day of genistein for one year was shown in one randomized controlled study. Genistein’s effect on BMD of the femoral neck and Ward’s triangle was actually greater than the increase in BMD due to use of HRT for one year, though both significantly increased BMD. Genistein increased BMD of the femoral neck, lumbar spine and Ward’s triangle significantly compared to placebo (Morabito, et al., 2002).

The Menfis randomized controlled trial involving 187 healthy postmenopausal women aged 39-60 years old in Southern Italy compared the BMD of women receiving HRT to those of women consuming an average of 47 mg/d of isoflavones over six months. There was a significant drop out of participants in the soy group and results were contradictory. However, there were no significant improvements in BMD in either the HRT or soy group, though, BMD did not decrease significantly as in the control group. Both groups showed slightly lower decreases of bone trabecular density compared to placebo. HRT was more effective in decreasing postmenopausal bone turnover. But a significant increase of osteoclast (marker for bone formation) was noted in the soy group, indicating stimulation of osteoblastic activity and suggesting a beneficial effect of soy on bone formation (Chiechi, et al., 2002).

In a similar study, focusing on the affect of consumption of isoflavone enriched foods on BMD and bone metabolism, isoflavones were found to have no effect. Consumption of 110 mg/d of soy isoflavone aglycone for one year by 237 healthy, non osteoporotic early postmenopausal women did not prevent postmenopausal bone loss and did not influence bone turnover rates when compared to placebo (Brink, et al., 2008). Rapid bone loss occurs shortly after menopause so a substantial preventative effect would be seen by isoflavones if they worked during this time period. Older postmenopausal women have already lost a significant amount of bone mass from
their first years of menopause and do not lose bone density as quickly, however, there are age related decreases in osteoblast renewal that contribute to bone loss in the older postmenopausal women. It has also been shown that the skeleton of women older than seventy is more sensitive to low dose estrogen treatment than that of younger women (Kenny, et al., 2009). The ability of soy to potentially act as a SERM may be more beneficial to older postmenopausal women in comparison to younger.

Two randomized controlled trials of postmenopausal women sixty years old or older, reported soy protein with soy isoflavones to have no affect on BMD (Kenny, et al., 2009; Kreijkamp-Kaspers, et al., 2004). A trial of 97 healthy older postmenopausal women, older than sixty years old found that soy protein and isoflavone intake, either in combination or alone did not affect BMD when compared to placebo protein intake over one year. No significant differences in BMD or bone turnover markers were found between the groups (Kenny, et al., 2009) The other trial of 175 healthy postmenopausal women aged 60-75 years measured BMD at thirteen various sites. The BMD of the intertrochanter region was significantly higher in the soy group compared to placebo. However the other twelve BMD measurements had no significant difference between groups. Analysis of years since menopause showed that women who had most recently started menopause had better results after the year of soy intervention when compared to those who were more remote from menopause; who did slightly worse compared to placebo. The difference however, did not reach statistical significance.

Studies involving both perimenopausal women and postmenopausal women have shown neutral results. In one clinical study soy isoflavones marginally affected bone turnover markers, such that the changes would be unlikely to be clinically relevant (Wangen, et al., 2000). Lastly, in a recent meta-analysis of 10 randomized controlled clinical trials, Between 40 and 110mg
isoflavones produced no change in BMD over a one year period in women of varying ages. The average intake of isoflavones was 88.8mg/day with most studies using close to 90mg and average length was just over 12 months with all but two studies (15 and 24 months) lasting 12 months (Liu, et al., 2009).

Bone mineral density and bone turnover markers are important tools in the analysis of bone health. Calcium metabolism is another factor, overlooked in the previous studies, that affects bone health. It is necessary to determine whether calcium metabolism is affected by soy or soy isoflavones because estrogen has been reported to increase calcium absorption and estrogen replacement therapy administered to postmenopausal women can return calcium absorption to premenopausal amounts. A randomized cross-over study involving fifteen postmenopausal women consuming either soy protein, soy isoflavones and soy protein or placebo resulted in no significant difference in calcium metabolism between the groups. The type and concentration of soy protein isolates and isoflavones used appears not to affect bone deposition, resorption, or balance in postmenopausal women who were beyond the phase of rapid bone loss. Biomarkers of bone turnover were also assessed and only osteocalcin was significantly greater in the soy protein only diet in comparison to placebo. No significant changes in bone turnover biomarkers were noted in the soy protein plus isoflavones group, though osteocalcin levels were intermediate. However each intervention was only twenty-eight days long and the women in the study were older with a mean age of 57. Also net calcium retention was not improved by the reduction of urinary calcium, which suggests that it is important to evaluate overall calcium metabolism rather than to rely exclusively on urinary calcium for predicting consequences to bone (Spence, et al., 2005).
**Cardiovascular Disease**

Epidemiological studies have suggested protective effects of soy isoflavones against a number of chronic diseases including, coronary heart disease. Asian countries with higher noted consumption of soy have lower rates of coronary artery disease when compared to Westerners (Blum, 2003). Isoflavones have been proposed to have lipid lowering effects as well as effects on vasodilation and arterial compliance (Aubertin-Leheudre, Lord, Khalil, & Dionne, 2008). These potential benefits on the cardiovascular system have been evaluated through several randomized controlled trials. Most of the trials have measured serum or plasma lipid levels as a determination of atherosclerotic risk and some incorporated other cardiovascular risk markers.

The American Heart Association (AHA) concluded that soy protein and soy isoflavones do not provide significant benefit for cardiovascular health. Furthermore, it noted no evident benefits of soy protein consumption on HDL cholesterol, triglycerides, lipoprotein(a), or blood pressure. Studies showing soy and soy isoflavones’ lack of effect on plasma lipid and lipoprotein levels supported the AHA’s decision (Sacks, et al., 2006). However, other cardiovascular risk markers should also be considered. Data suggests that genistein may have a preventative role in reducing CAD by acting as a SERM. Genistein has been shown to enhance dilator response to acetylcholine of atherosclerotic arteries, increase the ratio of nitric oxide to endothelin, and improve flow mediated endothelium dependent vasodilation in healthy postmenopausal women (Atteritano, et al., 2007). The FDA approved labels of consumer information saying that soy foods “may reduce the risk of heart disease”. This reduced risk is due to the lipid lowering benefits of soy; but these benefits have varied according to different studies (Teede, et al., 2001). Some have found significant benefits of soy on lipids, other have failed to.
Several randomized controlled trials have evaluated the effects of soy, soy isoflavones and genistein specifically, on plasma serum lipid levels. An epidemiological study involving 478 postmenopausal Japanese women with a mean intake of 54.3 mg/day of isoflavones found no significant difference in serum total cholesterol, serum triglycerides, LDL cholesterol, HDL cholesterol, apolipoprotein AI, B, and E between the highest and lowest intake of isoflavones. The results were consistent among early (<5 years) postmenopausal and late (>5 years) postmenopausal Japanese women (Somekawa, et al., 2001). Two randomized controlled trials came to similar conclusions. A one year trial comprised of 202 healthy postmenopausal women aged 60-75 years old who were assigned to consume either soy protein containing 99 mg of isoflavones comprised of: 52 mg genistein, 41 mg of daidzein, and 6 mg of glycerine, or placebo containing milk protein, daily found no statistically significant difference between the two groups (Kreijkamp-Kaspers, et al., 2004). A six month trial involving 50 obese postmenopausal women showed that 70mg/day of isoflavones (44 mg daidzein, 16 mg glycine and 10 mg genistein) had no favorable effect on risk factors of cardiovascular disease. Systolic blood pressure, diastolic blood pressure, HDL-C, LDL-C, total cholesterol, triglycerides, and HDL to total cholesterol ratio, were unaffected by supplementation of 70 mg/day of isoflavones (Aubertin-Leheudre, et al., 2008).

Other randomized controlled studies have found beneficial effects in conjunction with soy and isoflavone supplementation. Teede et al. showed that soy supplementation of 118 mg isoflavones with soy protein improved systolic and diastolic blood pressures and lipids in normotensive men (108) and postmenopausal women (105) aged 50-75 years old. LDL/HDL cholesterol ratio and triglycerides were significantly reduced in the soy group and the overall lipid profile was improved. However, Teede failed to show overall vascular function
improvements by isoflavones and noted increased levels of lipoprotein A (Lp A), and a decrease in mean brachial artery flow-mediated vasodilation, which is associated with negative cardiovascular effects (Teede, et al., 2001).

Compared to placebo, 54 mg/day of genistein significantly decreased fibrinogen levels, F2-isoprostanes, and sVCAM-1 (vascular cellular adhesion molecule) and sICAM (intracellular adhesion molecule) levels in a two year randomized controlled trial involving 389 osteopenic postmenopausal women. Levels of LDL, HDL and total cholesterol were not significantly changed and Lp A and triglycerides levels remained similar between groups (Atteritano, et al., 2007).

One last study evaluated the effectiveness of isoflavones cardioprotective capabilities by assessing inflammatory biomarkers of cardiovascular disease. This crossover study involved 117 European postmenopausal women taking isoflavone enriched supplements of 50 mg/day (2:1 ratio genistein to daidzein) or placebo for 8 weeks and then after a washout period of 8 weeks the groups switched. Isoflavone supplementation improved CRP (C-reactive protein) concentrations (OR 95% for CRP values >1mg/L) compared to placebo (0.43 0.27-0.69). No significant effects of isoflavone treatment were observed on: von Willebrand factor, intracellular adhesion molecule1, vascular cellular adhesion molecule 1, E selection, monocyte chemoattractant protein 1, CRP, and endothelin 1 concentrations. Circulating concentrations of these adhesion molecules are considered to be predictive of cardiovascular disease risk because they indicate a pro-inflammatory state in the vasculature. Though soy products had little effect on the majority of the biomarkers of cardiovascular disease, its effect on CRP suggests that there may be some basis for the recommendation of use of soy isoflavones for cardiovascular benefits for the healthy postmenopausal female. However the overwhelming evidence that soy or soy
Isoflavones have little effect on cholesterol, triglycerides, and blood pressure point to little to no positive cardiovascular benefit from soy.

The efficacy of soy and soy product supplementation in regards to cardiovascular health appears to be poor. Though many of the studies found some beneficial effects, alternative studies contraindicated their results. These discrepancies may be due to a variety of confounding factors including the length of supplementation, the amount of isoflavones given and whether they were given with soy protein or just as isoflavones. Also the varying quantities and combinations of the different isoflavones may play a role in why the results varied so greatly. Regardless of their specific effects, replacing a serving of red meat based protein with soy will provide cardiovascular benefits even if the isoflavones themselves do not add any specific lipid lowering capabilities.

**Breast Cancer**

Numerous epidemiological studies have investigated the association between soy isoflavones and breast cancer risk. As mentioned earlier, other than in animal studies, isoflavones have shown mostly positive effects or no effect on breast cancer. However, to be able to recommend soy isoflavone consumption as a potential preventative treatment, the efficacy of soy isoflavones must be established.

Epidemiological evidence suggests that soy isoflavones may have beneficial effects on the risk of developing breast cancer. Several meta-analyses have associated increased intake of soy with reduction of breast cancer risk (Qin, Xu, Wang, & Hoshi, 2006; Trock, et al., 2006; Wu, Yu, et al., 2008).

One meta-analysis included studies that varied significantly on their focused variables: menopausal status, forms of isoflavones consumed, and quantities of isoflavones were evaluated.
Studies looked at soy protein, tofu, bean curd consumption, and estimates of isoflavone intake, specifically genistein and daidzein intake. Consumption was also measured differently; some studies measured urinary excretion of specific isoflavones while others used food frequency questionnaires to estimate intake. After controlling for confounding factors, high soy intake was modestly associated with reduced breast cancer risk. Ten studies where then stratified by menopausal status, and an inverse association between soy exposure and breast cancer risk was noted with the highest significance in premenopausal women. A stronger protective effect was observed among Western women (OR= 0.84, 95% CI 0.70-1.00) in comparison to Asian women (0.89, 95% CI 0.71-1.12) (Trock, et al., 2006). Considered together these studies support the potential of a small reduction in breast cancer risk associated with intake of soy foods.

Wu’s meta-analysis described earlier, found a significant reduction in breast cancer rates that was dependent on dose. A 12% reduction in breast cancer risk was found when comparing the lowest rates of soy consumption with moderate levels and a 29% reduction when comparing the lowest rate with the highest levels of soy consumption. Contradicting the previous meta-analysis, reduced risk of breast cancer was found in both pre and postmenopausal women. Also, no protective effects were established in the Western studies, although their levels of isoflavone intake were relatively low in comparison to the Asian studies (Wu, Koh, et al., 2008).

The Singapore Chinese Health Study found significant reduction of risk with intake of 10.6 mg 1000Kcal -1 or more of soy isoflavones daily. Risk of breast cancer was reduced 18%. The reduction was significant for postmenopausal women but not premenopausal women with relative risks of 0.74 and 1.04 respectively. The reduction in risk was found regardless of estrogen and progesterone receptor status. Also of note, the protective effect of high soy intake
was clearly statistically significant among women who had been followed for 10 or more years (RR = 0.48, 95% CI = 0.29-0.78) (Wu, Koh, et al., 2008).

Among the epidemiological studies researched, soy and soy isoflavones were found to significantly decrease risk of breast cancer in three meta analyses (Qin, et al., 2006; Trock, et al., 2006; Wu, Yu, et al., 2008), three case controlled studies (Iwasaki, et al., 2008; Kim, Kim, Nam, Ryu, & Kong, 2008; Verheus, et al., 2008), and two cohort studies (Lee, et al., 2009; Wu, Koh, et al., 2008). Several studies found the relationship between soy and/or soy isoflavone consumption to be somewhat dose dependent although each had different dosing ranges. In general, the studies involving Asian women had more positive results in regards to reduction of breast cancer risk, although this is likely due to the high consumption of soy by Asians. Studies involving Westerners that had positive results, established results at lower levels of intake generally, compared to Asian studies. For example two nested case controlled studies; one using Dutch participants, another using participants from Japan found inverse associations between soy isoflavones and breast cancer risk although at different genistein levels. The Dutch study’s median control group genistein level was 3.75 ng/ml for premenopausal women and 4.89 ng/ml for postmenopausal women (Verheus, et al., 2008). In comparison the Japanese study’s control group median was 144.5 ng/ml (Iwasaki). In fact the range of intake was from 0 to 57.5 ng/ml for participants in the Dutch study while consumption of 57.5 ng/ml would not have made it into the participants or controls interquartile range of 67.9-255.6 for the Japanese study (Iwasaki, et al., 2008; Verheus, et al., 2008).

Studies varied on results according to menopausal status as well. More studies favored soy isoflavones and soy having a more significant effect on premenopausal women. In a case controlled study involving 724 pre and postmenopausal women, half with breast cancer,
premenopausal women had more significant positive results involving breast cancer risk. When adjusted for confounding factors, high soy protein intake was associated with reduced breast cancer risk among premenopausal women (OR=0.39 in the highest quartile, 95% CI 0.22-0.93, P for trend =0.03) more so than postmenopausal women (OR=0.22 in the highest quartile, 95% CI 0.06-0.88, P for trend =0.16). Total tofu intake also had an inverse association with breast cancer risk in premenopausal women (OR=0.23, 95% CI 0.11-0.48, P for linear trend <0.01) yet no association was found for postmenopausal women (Kim, et al., 2008). The Shanghai Women’s Health Study, involving 73,223 Chinese women found similar results. No significant association with soy food consumption was found for postmenopausal breast cancer yet a 43% reduction of risk of premenopausal breast cancer was found among those whose soy food intake during adolescence was in the highest intake group (Lee, et al., 2009).

Not all epidemiological studies found inverse associations between soy and breast cancer risk. One British study involving 37,643 women older than 20 years, included one-third vegetarians into their study because of proposed increased consumption of soy by non-meat-eaters. The baseline mean consumption of isoflavones was 2.9 mg/day for non-vegetarians compared to 10.2 mg/day for vegetarians. However, even in Westerners with increased levels of isoflavones comparatively, no significant associations were made. No strong association between vegetarianism or dietary isoflavone intake, and breast cancer risk was found (Travis, et al., 2008). Another Western study involving 45,448 premenopausal and postmenopausal Swedish women, who were followed for thirteen years, found similar results. No inverse association was found between dietary intake of isoflavones and risk of breast cancer, either overall or by ER/PR status. However the isoflavone intake in the study was low with a median intake of only 7 µg/d of isoflavone in both the groups with and without breast cancer (Hedelin, et al., 2008).
Other studies, instead of focusing on the risk of developing new onset breast cancer, focused the effect of soy consumption on women who had already been diagnosed with breast cancer. They looked at recurrence rates and death. The Shanghai Breast Cancer Survival Study involved 5,042 female breast cancer survivors in China aged 20-75 years old. They followed the women for a median of 3.9 years assessing the rates of breast cancer recurrence and risk of death associated with increased consumption of soy food. Soy food consumption was significantly associated with decreased risk of death and recurrence of breast cancer among this Chinese population of breast cancer survivors regardless of the estrogen receptor status of their breast cancer. The inverse association of soy protein and isoflavone intake with mortality and recurrence appears to follow a linear dose response pattern, similar to the studies evaluating risk of development of breast cancer. Hazard ratios comparing the highest quartile, which was greater than 62.68 mg/day of isoflavone intake, to the lowest quartile of soy isoflavone intake, which was less than 20 mg/day, were 0.79 (95% CI, 0.61-1.03) for mortality and 0.77 (95% CI, 0.60-0.98) for breast cancer recurrence (Shu, et al., 2009).

The LACE study also looked at risk of cancer recurrence with consumption of soy isoflavones. It was an epidemiological study that followed 1,954 female breast cancer survivors over 6.31 years. Non-significant decreased risk of breast cancer recurrence was noted with increasing intakes of both diadzein and glycetin though they were borderline significant for postmenopausal women specifically. Women in the highest daidzein and genistein intake categories had an approximately 50% reduction in breast cancer recurrence that was not significant. Increasing levels of isoflavones were associated with a decreasing risk of breast cancer recurrence among tumors that were ER+ and PR+ but not ER- or PR-. The LACE study was conducted in the US and the population of mostly Caucasian females had low consumption
of soy foods, with the highest quartile of genistein’s intake averaging only 1,022.9 µg/day. Though the results are not as impressive as the Shanghai study, suggestive trends for reduced risk of cancer recurrence were observed with increasing quartiles of isoflavones (Guha, et al., 2009).

Lastly, there are few randomized controlled trials involving soy isoflavone intake and markers for breast cancer. One such marker is mammographic density. Increasing densities are associated with a 4-6 fold increased risk of development of breast cancer. The results of two double-blind randomized controlled trials found no association between soy isoflavones and increasing or decreasing mammographic densities. The Osteoporosis Prevention Using Soy study included 406 postmenopausal women taking 80 mg or 120 mg a day of isoflavones or placebo. After two years, isoflavone supplementation did not significantly modify breast density (Maskarinec, et al., 2009). A Dutch study involving 202 postmenopausal women aged 60-75 years compared the effects of soy protein with 99 mg of isoflavones daily with placebo (milk protein). After one year mammographic density decreased in both the placebo group and isoflavone group, but the decrease did not differ significantly between groups. Soy protein and 99 mg of isoflavones did not significantly decrease the mammographic densities of these postmenopausal women (Verheus, et al., 2008). These two studies along with several others, relating to changes in mammographic density, do not support decreases in density due to isoflavone consumption. If isoflavones do, as the majority of epidemiological evidence points, cause beneficial decreases in breast cancer they must act through alternative routes other than decreasing breast tissue density.
Discussion

Soy and soy isoflavones are well researched topics with information regarding their effects on postmenopausal women. Epidemiological studies and randomized controlled trials have evaluated the efficacy of soy and soy isoflavones for treatment and prevention of breast cancer, prevention or reversal of bone loss, and benefits to the cardiovascular system.

Safety

In general, epidemiological evidence and several randomized controlled trials support the safety and potential health benefits of soy and soy isoflavones. There were discrepancies between studies, however, the overall conclusion was that soy and soy isoflavones were safe to use at doses similar to average Asian consumption. Mild side effects were noted with soy isoflavone use with gastrointestinal complaints being most common. Ten randomized controlled trials evaluated the safety profile of soy and soy isoflavones (Table 2). The studies varied in length from 84 days to three years, and in dosage of soy and isoflavones from 54 mg of genistein to 900 mg a day of isoflavones (Atteritano, et al., 2007; Marini, et al., 2008; Marini, et al., 2007; Morabito, et al., 2002; Pop, et al., 2008). One important note is that of the six studies that reported uterine and/or vaginal effects, none found a significant difference between placebo and treatment groups (Atteritano, et al., 2007; Brink, et al., 2008; Kenny, et al., 2009; Kreijkamp-Kaspers, et al., 2004; Marini, et al., 2007; Morabito, et al., 2002). Soy does not appear to be associated with the uterine issues which inhibits the use of estrogen only HRT treatments. These results were supported by a safety review which concluded; soy isoflavones as typically consumed in diets based on soy or containing soy products, where generally safe (Munro, et al., 2003).
However, some weaknesses in the studies are worth noting. First, the focus of the majority of the studies was not to independently evaluate the safety of soy. Many of the studies evaluated the efficacy of soy or soy isoflavones on some component of health. Therefore, the side effect profile was not comprehensively evaluated. Only one study focused specifically on soy safety and the safety of soy at high dosages (Pop, et al., 2008). This study assessed the safety of soy isoflavones, including both genistein and diadzein at combined levels of 900 mg, and provided the most comprehensive assessment of the safety of isoflavones although it was relatively short, lasting 84 days and only 30 participants successfully completed the trial (Pop, et al., 2008). The long term effects of soy were not established and the small subject size leads to increased risk for error. Other studies evaluated a less comprehensive safety profile for longer periods and at lower doses.

**Cardiovascular**

Epidemiologic evidence suggests that increased soy consumption is cardioprotective. However, none of the studies included in this review evaluated clinical cardiovascular events. In the six randomized studies, three supported some form of cardiovascular benefit to soy consumption and three found no association. Studies ranged in length from eight weeks to two years and isoflavone consumption ranged from 50-118 mg/day (Atteritano, et al., 2007; Hall, et al., 2005; Teede, et al., 2001). In general, most studies reported small to moderate effects on a limited number of biomarkers of cardiovascular disease. Soy was associated with improved blood pressure and improved lipid levels in one study and biomarkers fibrinogen and soluble intercellular adhesion molecule -1 and soluble vascular cellular adhesion molecule-1 in another (Atteritano, et al., 2009; Teede, et al., 2001). Though Teede found some cardiovascular benefits, overall vascular function improvements by isoflavones was not proven. Additionally, increased
levels of lipoprotein A (Lp A), and a decrease in mean brachial artery flow-mediated vasodilation, which are associated with negative cardiovascular effects were noted (Teede, et al., 2001).

Other studies provided mixed cardiovascular results. One study found soy to be associated with improved blood pressure and lipids; several other studies found no association between soy, lipids and blood pressure. No significant difference in serum total cholesterol, serum triglycerides, LDL cholesterol, HDL cholesterol, apoplipoprotein AI, B, and E was found between the highest and lowest intake of isoflavones (Kreijkamp-Kaspers, et al., 2004). In another study systolic blood pressure, diastolic blood pressure, HDL-C, LDL-C, total cholesterol, triglycerides, and HDL to total cholesterol ratio, were unaffected by supplementation of 70 mg/day of isoflavones (Aubertin-Leheudre, et al., 2008). Lastly the AHA’s recommendation that the FDA revoke the soy protein and CHD health claim and it’s statement that “…there are no evident benefits of soy protein consumption on HDL cholesterol, triglycerides, lipoprotein(a), or blood pressure. Thus, the direct cardiovascular health benefit of soy protein or isoflavone supplements is minimal at best” make any significant cardiovascular benefit difficult to argue (D. W. Jones, 2008).

Bone

A total of 10 trials evaluated the effect of soy and soy isoflavones on bone. The results were mixed. Soy may have some positive effect on either bone formation or the prevention of bone loss. The studies have been relatively short in duration, generally involved few subjects, and most examined markers of bone turnover and BMD. Several studies evaluated genistein specifically while others evaluated soy isoflavones with or without soy protein. Rates ranged from 54 mg genistein to 130 mg a day of soy isoflavones with soy protein (Marini, et al., 2008;
Wangen, et al., 2000). More positive results were seen in early postmenopausal and osteopenic women. Two studies involving both healthy early postmenopausal women and late postmenopausal women found no significant change in BMD with soy supplementation at levels of 110mg/d and 105mg/d of isoflavones for one year each (Brink, et al., 2008; Kenny, et al., 2009). Osteopenic postmenopausal women in one study had decreased levels of bone resorption markers (PYR, CTX and sRANKL) and increased new bone formation markers (B-ALP, IGF-I and OPG) through to the third year and showed genistein to increase net bone mass (Marini, et al., 2007). Soy appears to provide some beneficial effect on bone resorption and bone formation for osteoporotic or osteopenic postmenopausal women but likely has little beneficial effect on healthy postmenopausal women’s bone density and turnover.

**Breast Cancer**

Studies focusing on the effects of soy and soy isoflavones on the breast were plentiful. The majority of these studies found soy consumption to be associated with decreased rates of breast cancer or breast cancer recurrence despite variations in specific results. However, two studies found no difference in risk. These studies were in Caucasian populations and had lower levels of consumption comparatively to the other studies. One study followed the soy isoflavone consumption of 49,261 Swedish women for 13 years. Its participants had very low levels (less than 0.1mg/day) of isoflavone intake. With the low rate of consumption any effects of isoflavones would be difficult to determine. Also food consumption was only measured once, assessing the dietary habits of the women during the six months preceding enrollment in the study. The study was 13 years duration and there was risk for misclassification of women who changed their dietary intake during this period (Hedelin, et al., 2008). The other study involved British women and had larger rates of consumption of soy due to its high level of vegetarian
participants. British vegetarians consumed an average of 10.2 mg/day of soy which was substantially higher than their non-vegetarian counterparts. However only 31% of the participants were vegetarians and many vegetarians do not become vegetarian until adulthood so long term exposure to soy may not be accurate. Also, their food frequency questionnaire was not specifically designed to assess phytoestrogen intake and did not include isoflavones found as food additives (Travis, et al., 2008).

Trock’s meta-analysis of soy intake and risk of breast cancer was one of the key studies reviewed. Its greatest strength was that it was a large meta-analysis involving 18 studies. However the study was not without limitations. One of the most notable was the lack of heterogeneity of the data (Trock, et al., 2006). Most of the studies were not originally designed to evaluate the risk of breast cancer in association with soy intake. Also, particularly in the Western studies used, selection bias was of concern.

The LACE study was one of the key studies that reviewed the risk of cancer recurrence in association to soy isoflavone intake in a Western population. It assessed how soy isoflavone consumption and tamoxifen therapy affected recurrence rates. It found increasing isoflavone intake to decrease the risk of recurrence of cancer among tumors that were ER + and PR+ but not ER- and PR- in breast cancer survivors. It also found a sixty percent reduction in breast cancer recurrence when comparing the highest to lowest diadzein intakes of postmenopausal women treated with tamoxifen. It show decreased recurrence rates with soy consumption and continued to show decreased recurrence with the addition of tamoxifen treatment. One limitation of this relatively large (1,954 female breast cancer survivors) and long (6.31years) cohort study was the high percentage of Caucasian participants with low consumption of soy food. The average intake of soy in this study was significantly lower than Asian populations. The study also had
incomplete reporting of specific supplement brand names and therefore was unable to quantitatively account for soy isoflavones received via supplementation. However, few women reported using supplements accounting for only 53 out of the 1,954 participants. Lastly, though participants were screened to make sure they were free of recurrence via self report, no mammogram or exam was used to confirm the participants’ breast cancer free status (Guha, et al., 2009).

Another important study was the Shanghai Breast Cancer Survival Study, a large cohort study (n=5,042) of Asian breast cancer survivors followed for a median of 3.9 years. It found greater risk reduction in premenopausal breast cancer occurrence compared to postmenopausal breast cancer. No significant association with soy food consumption was found for postmenopausal breast cancer yet a 43% reduction of risk of premenopausal breast cancer was established. The follow up was relatively short, with a range of 0.5 to 6.2 years so evaluation of long term effects of soy intake on breast cancer recurrence cannot be drawn from this study. One noteworthy limitation of this study was the potential for reverse causation. Women who had subclinical recurrence would be more likely to have poor appetite and potentially therefore consume less soy (Lee, et al., 2009). However this was a potential limitation of several other studies involving soy consumption in women with breast cancer.

The long term exposure of Asian women to soy foods during childhood and adolescence may be a possible reason for the Asian epidemiological studies reporting decreased breast cancer rates. No randomized controlled trials involved children or adolescents and few studies incorporated soy intake averages from childhood. Those that did were at risk of recall bias. If early life is a critical period for soy consumption then the majority of these studies which focused on pre- and postmenopausal women may not have captured the association with breast
cancer risk and could underestimate the association in Asian women. Lastly, because Caucasian women would have been less likely to have high consumption of soy as children and adolescents it may be that the lower levels of soy intake in adulthood may be comparatively more important in affecting risk of breast cancer. This may explain the results seen in some Western studies with relatively low soy and isoflavone intake comparatively.
Limitations

Epidemiological studies provided the majority of information regarding the safety and efficacy of soy and soy isoflavones. In general, epidemiological studies are weaker quality of evidence due to the potential for error selection, bias, and confounding factors. Randomized controlled trials and meta-analyses provided higher quality evidence, and in some instances additional limitations.

Limitations include a lack of continuity between studies. The key beneficial component of soy foods is unknown. There are diverse theories postulating which component is most important and this accounts for a wide range of controlled variables. Studies evaluated a variety of soy components both individually and in combination, with varying results between substances. For example, some studies measured soy, others soy protein, or phytoestrogens, and combinations of them all. Another limitation was the lack of a common dosage pattern between studies. Because the test variables were different in each study so were the dosages and combinations of soy components. The lack of a standard dose or dose pattern also limited the ability for comparison because results found with the high doses were not always found with lower doses. Dose response patterns were difficult to validate; some studies had linear response rates while others had no effect with high doses and still other studies with substantially smaller doses did see effects.

One other reason for the variability between studies could be the measurement methods used. There was significant variety in the methods used to measure soy or soy isoflavone consumption. Many of the studies used food frequency questionnaires to measure their participants’ soy product intake. This method allows for recall bias by the participant. It also limited the participant’s choice by restricting them to a specific list of product options for
measuring their soy and soy isoflavone consumption. Those with consumption of soy products not on the prefabricated list may have had inaccurate soy consumption values. Lastly, these questionnaires did not allow for the variations in quantity of soy and soy products in foods. This again could affect the end rate of soy consumption for participants.

Intake of soy products was measured by all the studies. However, very few studies measured the absorption and metabolism of soy and isoflavones. The difference between consumption and absorption of various soy products may play an important role in determining the efficacy of soy and soy isoflavones on the female body. The studies that did measure absorption varied in their methods. Some studies measured urine and others measured blood serum. These tests are time sensitive and vary greatly depending on the last time of consumption of soy products so it is necessary not only to measure these values but to regulate the timing of the last consumption of soy products. Lastly, no study directly compared the effects of soy by ethnicity. The majority of the studies used Asian or Caucasian participants, but failed to directly compare at similar consumption levels, the effect of soy on Asians in contrast to Caucasians. Ethnicity may affect the metabolism or absorption of soy products and be an important variable in evaluating the results of soy consumption.

These limitations coupled often with small sample sizes or short durations of treatment may have affected the results of many of the studies reviewed. The discrepancies between studies may be due to a variety of confounding factors including the length of supplementation, the quantities and combinations isoflavones given and whether they were given with soy protein or as isoflavones. Lastly, the metabolism and absorption of isoflavones may alter their efficacy.
Conclusion/Future Research

Soy appears to be safe for consumption based on epidemiological and experimental data and long term consumption of soy in Asian countries with a long lifespan and low cancer rates. Given the widely positive findings for soy consumption over various lengths and wide ranges of quantities it is likely that soy and the isoflavones found within it can be consumed safely as a part of a balanced diet. Pre and postmenopausal women, even those with breast cancer or a history of breast cancer can probably safely consume soy products at quantities similar to those found in Asian diets. However, more evidence is needed before recommendation of soy consumption can be made for breast cancer survivors, particularly those taking tamoxifen.

It appears that increased soy intake may be associated with decreased breast cancer rates but to what extent is still undetermined. With much of the support for soy’s efficacy in reduction of breast cancer coming from epidemiological and observational studies the complete impact of soy on the breast has not been evaluated. The concern that soy isoflavones might be contraindicated for patients with breast cancer or increased risk of breast cancer is almost exclusively based on results from animal studies. Randomized controlled trials are necessary for definitive recommendation. Though there is evidence that soy may have some preventative capabilities in regards to breast cancer occurrence and also may decrease breast cancer recurrence, at this time the existing data are not sufficiently strong enough to justify the use of soy foods in the treatment of breast cancer patients. However, the growing epidemiological and clinical data suggests that soy consumption is likely to produce some beneficial effect on the occurrence of breast cancer and including it as part of a balanced diet may be a beneficial recommendation for healthy pre and postmenopausal women.
The cardiovascular benefits of soy appear to be minor. Limited evidence and lower quality studies along with the variety of biomarkers used to evaluate soy’s cardiovascular effects provided diverse outcomes on the effects of soy on the cardiovascular system. In fact, no study evaluated clinical cardiovascular events. Soy and soy isoflavones are likely to provide limited benefit to cardiovascular outcomes on their own. However, as a replacement of other higher cholesterol animal protein sources, soy is likely to be part of a healthy heart diet. Though little direct benefit from soy consumption was observed the benefits in its use as a replacement to other proteins including red meat, and its lack of negative effects on cardiovascular markers make it an acceptable alternative to the less desirable protein choices.

Lastly, soy’s effects on bone seem to be inconsistent and although it may reduce bone loss, it does not appear to be more effective than current treatments available so its use in clinical practice would likely be limited. In conclusion, soy appears to be beneficial for osteopenic postmenopausal women but likely has little beneficial preventative effect on healthy postmenopausal women’s bone density and turnover. However, further research is needed to validate this.

Further research is needed, particularly in regards to the ability of soy to act as a SERM and what effects soy has on the breast, cardiovascular system, and bone. More research is needed to determine whether the beneficial effects of soy food consumption are due to soy isoflavones, other soy constituents or the combination of them all.
References


### Proposed Isoflavone Anti-carcinogenic Mechanism of Action Independent of Estrogen Receptor Binding

<table>
<thead>
<tr>
<th>Mechanisms with direct hormonal effect</th>
<th>Mechanisms of no hormonal effect</th>
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<tbody>
<tr>
<td>5 α reductase inhibition</td>
<td>Antioxidant</td>
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<td>17 β hydroxysteroid dehydrogenase inhibition</td>
<td>Cell adhesiorr effects</td>
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<td>Aromatase inhibition</td>
<td>DNA topoisomerase inhibition</td>
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<td>Enhancement of immune system function</td>
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<td>Inhibition of cell proliferation*</td>
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<td>Inhibition of inflammation*</td>
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Modified from Velentzis *Lee
### Side effects reported with soy Isoflavone use at various dosages

<table>
<thead>
<tr>
<th>Name</th>
<th>Length (month)</th>
<th>n=</th>
<th>dose</th>
<th>Results - soy</th>
<th>Placebo</th>
</tr>
</thead>
</table>
| Atteritano         | 24             | 389 | 54mg/d genistein      | N=198  
- Abdominal pain (6)  
- Epigastric pain (5)  
- Dyspepsia (9)  
- Vomitting (4)  
- Constipation (13)  | N= 191 
(6)  
(5)  
(9)  
(4)  
(13) |
| Brink              | 12             | 237 | 110mg/d isoflavones   | Total cholesterol, LDL, HDL, Triacycglycerols  
Total leukocyte count  | Same as soy |
| Gleason            | 6              | 30  | 100mg/d isoflavones   | N=15  
- Breast or abdominal tenderness (2)  
- Excessive fatigue (4)  
- Loss of appetite (2)  
- Muscle weakness (3)  
- Nausea (3)  
- Pedal edema, calf tenderness, redness or swelling (2)  | N= 15 
(2)  
(4)  
(2)  
(3)  
(3)  
(2) |
| Kenny              | 12             | 97  | Soy protein +105mg isoflavone aglycone  
Soy protein 105mg/d isoflavone | Endometrial thickness  
GI disturbances (10)  
Differences in mammogram or breast tenderness (2)  
New onset cardiac symptoms (2)  
Increased BP (4)  
Respiratory infections (3)  
Unrelated medical conditions (4)  | Rates did not differ between groups |
| Kreijkamp-Kaspers  | 12             | 202 | 25.6g soy protein with 52mg genistein and 41mg diadzein | N=100  
- GI complaints (48)  
- Musculoskeletal complaints (68)  
- Lower and Upper airway complaints including ENT (62)  
- Urogenital complaints (16)  
- Dermatological complaints (29)  
- Miscellaneous (30)  | N=102 
(33)  
(68)  
(62)  
(16)  
(29)  
(30) |
| MacGregor          | 3              | 72  | 70mg/d isoflavones    | N=36  
- Constipation (2)*  
- Flatulence (1)*  
- Nausea (2)*  
- Headache (2)*  | 36  
(1)*  
(1)*  
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(1)* |
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<td></td>
<td>Dyspepsia (9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Vomiting (4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Constipation (13)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Creatinine</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Liver enzymes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pancreatic enzymes</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>389</td>
<td>N=191</td>
</tr>
<tr>
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<td>36</td>
<td>138</td>
<td>(3)</td>
</tr>
<tr>
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<td>(6)</td>
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<table>
<thead>
<tr>
<th><strong>Morabito</strong></th>
<th>54mg/day genistein</th>
<th>N=30</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Endometrial thickness &gt;5mm (3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vaginal bleeding (1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Breast tenderness (3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hot flushes (6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N=30</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(1)</td>
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</tr>
<tr>
<td></td>
<td>(1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(12)</td>
<td></td>
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<table>
<thead>
<tr>
<th><strong>Pop</strong></th>
<th>900mg isoflavones</th>
<th>N=18</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Increased BP (2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Increased AST (1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Increased triglycerides (1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Increased estrogen (0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Decreased FSH/LH (0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Increased TSH (0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Decreased T4 (1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Flatulence (0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N=12</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(0)</td>
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<td></td>
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</tr>
<tr>
<td></td>
<td>(1)</td>
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</tr>
<tr>
<td></td>
<td>(1)</td>
<td></td>
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<tr>
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<td>(1)</td>
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<tr>
<td></td>
<td>(4)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(1)</td>
<td></td>
</tr>
</tbody>
</table>

* N= number of participants who rated SE as worst
## Changes in BMD with soy or soy isoflavone supplementation

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Length</th>
<th>Soy type and quantity</th>
<th>Lumbar Spine BMD change</th>
<th>Femoral neck BMD change</th>
<th>Wards triangle BMD change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mont h</td>
<td>Soy</td>
<td>Soy</td>
<td>Placebo</td>
<td>Soy</td>
</tr>
<tr>
<td>Kenny</td>
<td>47</td>
<td>12</td>
<td>Soy protein + 35 mg isoflavones (n=25)</td>
<td>0.004 ± 0.009</td>
<td>0.010 ± 0.007</td>
<td>0.001 ± 0.008</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Placebo- Control protein with 50% sodium caseinate, 25% whey protein, 25% egg white protein (n=22)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N=150 0.024 (0.012-0.034)</td>
<td>N=154 -0.027 (-0.038-0.015)</td>
<td>N=150 0.016 (0.007-0.023)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>24</td>
<td></td>
<td>0.049 (0.035-0.059)</td>
<td>-0.053 (-0.058 to -0.035)</td>
<td>0.035 (0.025-0.042)</td>
</tr>
<tr>
<td>Marini</td>
<td>304</td>
<td>12</td>
<td>54 mg/d Genistein (n=150)</td>
<td>3% (± 2%)</td>
<td>-1.6% (±0.3%)</td>
<td>3.6% (± 3%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Placebo (n=154)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N=150 0.024 (0.012-0.034)</td>
<td>N=154 -0.027 (-0.038-0.015)</td>
<td>N=150 0.016 (0.007-0.023)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>24</td>
<td></td>
<td>0.049 (0.035-0.059)</td>
<td>-0.053 (-0.058 to -0.035)</td>
<td>0.035 (0.025-0.042)</td>
</tr>
<tr>
<td>Morabito</td>
<td>90*</td>
<td>12</td>
<td>54mg/day Genistein (n=30)</td>
<td>3% (± 2%)</td>
<td>-1.6% (±0.3%)</td>
<td>3.6% (± 3%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Placebo (n=30)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N=150 0.024 (0.012-0.034)</td>
<td>N=154 -0.027 (-0.038-0.015)</td>
<td>N=150 0.016 (0.007-0.023)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.049 (0.035-0.059)</td>
<td>0.035 (0.025-0.042)</td>
<td>-0.037 (-0.044 to -0.027)</td>
</tr>
<tr>
<td>Kreijkamp-Kaspers</td>
<td>175</td>
<td>12</td>
<td>25.6 g isoflavone soy protein (52mg genistein, 41mg daidzein, and 6 mg glycitein) (n=88)</td>
<td>-0.003</td>
<td>-0.004</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>25.6 g milk protein placebo (n=87)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

*30 participants received HRT. (Lumbar Spine BMD change =3.8 ±2.7%), (Femoral neck BMD change= 2.4 ±2%), (Ward’s Triangle BMD change= 3 ± 2%)*
Changes in Lipid profile with supplementation of Soy vs Placebo

<table>
<thead>
<tr>
<th>Author</th>
<th>N=</th>
<th>Length months</th>
<th>Soy type</th>
<th>Placebo Change from baseline (mg/dl)</th>
<th>Genistein Change from baseline (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teede</td>
<td>213</td>
<td>3</td>
<td>(40 g soy protein and 118 mg isoflavones)/day</td>
<td>Total Cholesterol -15.47 ± 3.48</td>
<td>Total Cholesterol -21.27 ± 3.48</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LDL -10.83 ± 2.71</td>
<td>LDL -16.24 ± 2.71</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HDL -4.25 ± 1.55</td>
<td>HDL -1.55 ± 1.16</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LpA 4 (-22-30)</td>
<td>LpA 42 (17-67)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Triglycerides -0.39 ± 1.93</td>
<td>Triglycerides -7.35 ± 1.93</td>
</tr>
<tr>
<td>Atteritano</td>
<td>389</td>
<td>12</td>
<td>54 mg/day genistein</td>
<td>Total cholesterol -0.02 ± ?</td>
<td>Total cholesterol -0.79 ± ?</td>
</tr>
<tr>
<td>Genistein</td>
<td></td>
<td></td>
<td></td>
<td>HDL +1.3</td>
<td>HDL +1.04</td>
</tr>
<tr>
<td></td>
<td>198</td>
<td></td>
<td></td>
<td>LDL -1.57</td>
<td>LDL -1.97</td>
</tr>
<tr>
<td>Placebo</td>
<td>191</td>
<td></td>
<td></td>
<td>LpA -0.1</td>
<td>LpA -0.97</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Triglycerides -5.52</td>
<td>Triglycerides +0.75</td>
</tr>
<tr>
<td>Atteritano</td>
<td>389</td>
<td>24</td>
<td>54mg /day genistein</td>
<td>Total cholesterol +3.19</td>
<td>Total cholesterol +2.28</td>
</tr>
<tr>
<td>Genistein</td>
<td></td>
<td></td>
<td></td>
<td>HDL +2</td>
<td>HDL +2.77</td>
</tr>
<tr>
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<td>198</td>
<td></td>
<td></td>
<td>LDL +0.3</td>
<td>LDL -1.17</td>
</tr>
<tr>
<td>Placebo</td>
<td>191</td>
<td></td>
<td></td>
<td>LpA +1</td>
<td>LpA 0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Triglycerides -2.65</td>
<td>Triglycerides +3.44</td>
</tr>
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</table>
## Soy Isoflavones and effects on Mammographic densities

<table>
<thead>
<tr>
<th>Name</th>
<th>N=</th>
<th>Length (year)</th>
<th>Menopausal status</th>
<th>Soy type and quantity</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maskarinec</td>
<td>358</td>
<td>2</td>
<td>postmenopausal</td>
<td>80 mg or 120 mg of isoflavones (42% daidzin, 2% daidzein, 13% genistin, 1% genistein, 39% glyctin, and 3% glycitein)</td>
<td>Isoflavones supplementation did not influence mammographic density in comparison to placebo at doses of 80 mg and 120 mg</td>
</tr>
<tr>
<td>Maskarinec</td>
<td>220</td>
<td>2</td>
<td>premenopausal</td>
<td>2 servings of soy (~25 mg of isoflavones and corresponded to 180 g soymilk, 126 g tofu, a 58 g soy protein bar, 31 g soy protein powder, or 23 g roasted soy nuts)</td>
<td>After 2 y of intervention no significant differences in mammographic densities by intervention status were observed but the mean percentage density had decreased by 2.8 and 4.1% in intervention and control women, respectively.</td>
</tr>
<tr>
<td>Maskarinec</td>
<td>514</td>
<td>½ premenopausal ½ postmenopausal</td>
<td>varied</td>
<td></td>
<td>An inverse relation between self-reported soy food intake and the size of the breast, in particular the nondense area was found yet soy intake and percent mammographic densities were positively associated.</td>
</tr>
<tr>
<td>Verheus</td>
<td>202</td>
<td>1</td>
<td>postmenopausal</td>
<td>36.5 g of Soy protein containing 99 mg of isoflavones (52mg genistein, 41 mg daidzein, 6 mg glycitein)</td>
<td>No changes mammographic density were observed between isoflavone supplementation and placebo. The decrease in mammographic density was similar to placebo.</td>
</tr>
</tbody>
</table>
Abstract

Objective: To determine if soy isoflavones are safe and efficacious for women as an alternative to HRT for breast, bone, and cardiovascular health.

Methods: The PubMed and CINAHL databases and the Cochrane library were searched using terms: soy foods, soy products, isoflavones, genistein, diadzein, premenopausal, postmenopausal, breast neoplasm, breast cancer, mammogram, and any combination of the aforementioned terms.

Results: Searches identified 25,756 titles; from these and multiple sub searches 35 studies were identified: four meta analyses, 16 randomized controlled trials, four randomized cross-over trials, eight cohort studies and three case controlled studies.

Conclusion: Soy and soy isoflavones appear to be safe and well tolerated in healthy postmenopausal women. Beneficial effects were found for osteopenic postmenopausal women, and for preventing breast cancer and recurrence (10 mg/day of soy isoflavone intake). Minimal cardiovascular benefit and no beneficial preventative effect on bone density or turnover in healthy postmenopausal women was found.