Soybean Isoflavones as an Alternative to Traditional Hormone Replacement Therapy: Are We There Yet? ¹

Gregory L. Burke,² Mara Z. Vitolins and Deirdre Bland*  

Departments of Public Health Sciences and Obstetrics and Gynecology, Wake Forest University School of Medicine, Winston-Salem, NC

Because of the high rates of chronic disease observed in postmenopausal women, the efficacy of different types of hormone replacement therapy (HRT) to reduce the burden of cardiovascular disease, osteoporosis, vasomotor symptoms and reproductive cancer in older women warrants investigation. This paper attempts to contrast the profile of traditional HRT with soy isoflavones (naturally occurring estrogen-like compounds found in soy).

Observational studies and clinical trials of HRT in postmenopausal women have generally shown a beneficial effect on cardiovascular disease risk, a significant improvement in bone density, a reduction in the number and severity of vasomotor symptoms (e.g., hot flashes or night sweats) and a potential beneficial effect on cognitive decline and dementia in older adults (Barrett-Connor and Grady 1998, Yaffe et al. 1998). In terms of adverse effects, long-term HRT use is associated with an increased risk of breast cancer (Colditz et al. 1995); an increased risk of endometrial cancer is observed in women with a uterus, which necessitates the addition of progestins to the estrogen regimen (Barrett-Connor and Grady 1998), and there exists an increased short-term risk of thromboembolic events in women with existing cardiovascular disease (Hulley et al. 1998). Data from population-based studies suggest that only 12–21% of U.S. postmenopausal women currently use HRT, suggesting that there is a large group of women who either will not or cannot use HRT (Manolio et al. 1993, Nabulsi et al. 1993). Because of this mixed picture for HRT, efforts are underway to identify agents that may have a better risk/benefit profile.

Countries consuming large amounts of soy have an improved chronic disease burden compared with countries consuming very little soy (Boring et al. 1994, Thom et al. 1992). Specifically, Japanese women have fourfold lower rates of cardiovascular disease mortality and breast cancer mortality, lower endometrial cancer rates and reported vasomotor symptoms that are nearly 10-fold lower than in U.S. or other Western women. Importantly, studies in migrants suggest that Japanese migrants to the U.S. mainland approach the rates of the cardiovascular and reproductive cancer of U.S. women (Robertson et al. 1977).

An intriguing property of soy isoflavones is their modest agonist effect on the $\beta$ estrogen receptor (approximately one third as potent as estradiol) and weak effect on the $\alpha$ estrogen receptor (0.001 as potent as estradiol) (Kuiper et al. 1998). Thus, soy isoflavones can be viewed as a type of selective estrogen receptor modulator. Randomized trials have been conducted to assess the effects of soy isoflavones on chronic disease. Specific findings include beneficial effects on lipids and lipoproteins, with a decline in total cholesterol (9%), LDL cholesterol (13%), and triglycerides (11%) and an increase in HDL cholesterol (2.4%) (Anderson et al. 1995). Animal studies have shown a beneficial effect on reducing atherosclerotic burden in coronary arteries of nonhuman primates (Anthony et al. 1997). Soy isoflavones appear to have only a modest beneficial effect on bone density in human studies, whereas animal models (often using higher doses) suggest a larger effect on bone density (Arjmandi et al. 1998). Effects on vasomotor symptoms have been mixed. A few studies using higher doses of isoflavone (50–80 mg/d), enrolling women with more vasomotor symptoms at baseline (4– 7 symptoms/d) and with larger sample sizes, have shown mildly beneficial effects on self-reported frequency and severity of vasomotor symptoms (Albertazzi et al. 1998, Washburn et al. 1999). However, it is important to note that at the doses tested, the effects on vasomotor symptoms are much smaller than those observed with traditional HRT. The data for soy isoflavones on breast cancer risk suggest either a neutral or a mildly beneficial effect on risk (Messina 1999). Evidence in both human and animal models suggests that soy isoflavones do not increase endometrial proliferation (Cline and Hughes 1998). For cognitive decline and soy isolate intake, scientific data are mixed. Uncontrolled observational studies suggest that increased tofu in the diet was associated with declines in cognition in a study of Japanese American men in Hawaii (White et al. 1996). Animal data suggest that there may be a

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² To whom correspondence should be addressed.
beneficial effect of soy isoflavones on neuroanatomy and simple memory tasks (Pan et al. 1999). This issue remains unclear, because no human trial data are available documenting the short- or long-term effects. Current evidence suggests that isolated soy protein and isoflavones are well tolerated with no evidence of bleeding, breast tenderness or gastrointestinal symptoms in postmenopausal women.

There are a number of subgroups for whom very few data are available on the potential risk or benefit from soy-containing isoflavones. No data are available documenting whether isoflavones will have a beneficial or detrimental effect in women with a history of breast cancer. In women with osteoporosis and osteoporotic fractures, the current evidence suggests that the effect in the beneficial effect of HRT and the relatively mild effects of soy, these women should not be encouraged to consider soy isoflavones as a viable alternative for treating their disease.

### Summary and Suggested Recommendations

In an attempt to compare the effects of soy isoflavones and traditional HRT, the current scientific data are summarized in Table 1. Beneficial effects on cardiovascular disease were observed with soy isoflavones and traditional HRT; menopausal symptom and osteoporosis relief are significantly greater with HRT, and no adverse effect on breast or endometrial cancer is present with soy isoflavones. Few data exist on the effect on cognition with soy isoflavones (e.g., bleeding, breast tenderness or headaches). Taken in aggregate, soy isoflavones should not be viewed as a viable alternative to traditional HRT on the basis of current data. It is important to note that a large number of excellent randomized clinical trials assessing both dietary soy supplements and isoflavone pills are underway at present. When these trials are completed, we may be better able to reevaluate the issue of soy isoflavones as an alternative HRT.

On the basis of the current evidence, we suggest that a healthful diet should contain one serving of soy per day. This recommendation is in agreement with the current recommendations of the American Heart Association, National Cancer Institute and American Dietetic Association. We believe that the use of isoflavone supplements is premature because of a paucity of data on both the efficacy and safety of these agents and the greater potential for intake of unsafe megadoses.

### LITERATURE CITED


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<th>Outcome</th>
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