A Review of the Evidence for the Use of Phytoestrogens as a Replacement for Traditional Estrogen Replacement Therapy

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Estrogen replacement therapy (ERT) is recommended for postmenopausal women primarily for reduction of menopausal symptoms and prevention of osteoporosis and cardiovascular disease. However, only 35% to 40% of women ever start ERT, and many do not continue it. One of the reasons women are reluctant to receive postmenopausal ERT is that they perceive prescription estrogens as being “unnatural.” Because of this, there is increasing interest in the use of plant-derived estrogens, also known as phytoestrogens. This article reviews the evidence for the potential of phytoestrogens, either in dietary or supplemental form, to replace traditional forms of ERT. A comprehensive search of the English-language literature identified more than 1000 articles published in the past 30 years about phytoestrogens. In total, 74 studies were selected for inclusion in this review based on relevance, inclusion of human subjects wherever possible, and study design. The studies examine phytoestrogens’ inhibition of the growth of cancer cell lines in vitro and in animals. They also look at the role of phytoestrogens in the reduction of cholesterol levels, and the use of one phytoestrogen derivative, ipriflavone, in the prevention of osteoporosis. Some small studies examine the role of phytoestrogens in the prevention of menopausal symptoms. Evidence for the potential health benefits of phytoestrogens is increasing. However, the clinically proven health benefits of prescribed ERT far outweigh those of phytoestrogens. Therefore, there is insufficient evidence to recommend the use of phytoestrogens in place of traditional ERT, or to make recommendations to women about specific phytoestrogen products.

Arch Intern Med. 2001;161:1161-1172

Postmenopausal estrogen replacement therapy (ERT) has been used for more than 25 years and combined estrogen-progesterone therapy has been widely used for at least the last 15 years. In this article, ERT will be used to refer to both estrogen and combined estrogen-progesterone replacement therapy. Current knowledge of ERT comes from large observational studies, cohort studies, and randomized controlled trials. Results of these studies show that, if used for primary prevention, ERT is associated with reduced mortality from cardiovascular disease by about 35%,1,2 reduces osteoporosis risk by about 50%,3 and reduces menopausal symptoms.4 Smaller studies suggest that ERT may also improve or reduce the incidence of such diverse medical conditions as memory loss,5 Alzheimer disease,6 tooth loss,7 and colon cancer.8 This list is not exhaustive and continues to expand as further studies are performed. Disadvantages of ERT include a potential increase in the risk of breast cancer (relative risk seems to be about 1.3 after at least 8 years of ERT9) and an increase in vaginal bleeding.10 There is an increased risk of endometrial cancer if women with an intact uterus take unopposed estrogen therapy. However, this risk is negated by the use of combined estrogen-progesterone therapy.11

The potential public health effect of ERT is reduced because only about 35% to 40% of menopausal women ever begin ERT and only about 15% continue taking it long-term.12 There are numerous reasons for this low uptake including physi-
cian failure to endorse and patient factors such as fear of breast cancer, disliking the adverse effect of vaginal bleeding, and the concept of interfering with a “natural” process.13,14

There has been a rapid increase in consumer interest in the use of alternative medicines, particularly in the use of supplements and herbs for the treatment of menopausal symptoms.13 It is reported that 70% of the patients who use complementary therapy do not reveal this to their “traditional” primary care physician because they either do not consider it a medicine or fear primary care physician disapproval.15

When deciding to take complementary therapies, patients frequently base their decisions on anecdotal reports of success in the lay literature more than information from scientific experiments. Many women who are unwilling to take traditional ERT see herbal therapies as natural and, therefore, preferable to “unnatural” prescription medication, despite the fact that traditional ERT is often derived from natural sources such as mare’s urine. Herbal and plant-derived therapies are frequently considered safer, although there are no government standards controlling their quality.16 While herbal supplements may be effective, they may also be dangerous, mixed with contaminants, or have unknown or adverse effects.17

Alternative medicines that are used for menopause include phytoestrogens, herbs, and nutritional supplements. Herbs traditionally recommended for menopausal symptoms include black and blue cohosh, evening primrose oil, chasteberry, and licorice. Vitamin E is a commonly recommended dietary supplement. A recent review article on these herbs and supplements reveals that the scientific evidence is scant regarding their safety and efficacy.18 Few randomized controlled trials have been done investigating their use and these trials show that none have proved better than placebo.19,22

Phytoestrogens are naturally occurring plant estrogens that have a chemical structure similar to human estrogen and that have the proven ability to attach to estrogen receptors in humans. Interest in these phytoestrogens (referred to in the lay literature as “natural estrogens” or “plant estrogens”) as an alternative treatment for menopause recently has increased. Increasing the intake of dietary phytoestrogens is thought to decrease the risk of cancer and cardiovascular disease. Concentrated phytoestrogens are available in pill form and are sold extensively in health food stores and on the Internet. Web sites attest to the fact that these supplements are natural, identical to human hormones, and as effective as prescription ERT. It is claimed that these supplements can lower cholesterol levels, reduce menopausal symptoms, decrease the risk of endometrial cancer, improve sexual enjoyment, and reduce the risk of osteoporosis.

This review summarizes the available published experimental data about the possible benefits and adverse effects of phytoestrogens to see if there are sufficient data to substantiate these claims. We compare this evidence with the known benefits and adverse effects of prescribed ERT. Based on the available scientific data, is there evidence that phytoestrogens could replace traditional ERT?

METHODS

The MEDLINE, CINAHL, and Cochrane databases from January 1, 1966, through September 30, 1999, were searched for articles using the terms “phytoestrogen,” “isoflavones,” “coumestans,” “lignans,” and “soy,” and cross-referenced with the terms “cholesterol,” “hyperlipidemia,” “endometrial cancer,” “breast cancer,” “osteoporosis,” “hot flashes,” “coronary heart disease,” “menopause,” and “prevention.” The reference lists of published articles were searched for relevant English-language articles about phytoestrogens that were not found on the database searches. Lay literature concerning phytoestrogens was obtained through Internet searches, and directly from the companies who supply plant-derived estrogens in pill form.

Criteria for the selection of articles included English language and human subjects wherever available. As far as possible, we endeavored to consider only evidence from randomized, blinded, controlled studies in preference to observational or epidemiological studies. Animal studies were included to support human data or if there were no relevant human studies available. In vitro studies were used to support animal or human data, or if there were no in vivo data available. As the interest in phytoestrogens has increased, the number of studies has also increased. Where important, the weakness in the trials and experiments cited are noted. Using these criteria, a total of 74 articles were considered relevant.

WHAT ARE PHYTOESTROGENS?

Phytoestrogens are a diverse group of nonsteroidal plant compounds that can behave as estrogens and occur naturally in most plants, fruits, and vegetables.23 They were first noted in 1926 to have estrogenic activity.24 Because they possess a phenolic ring, this enables them to bind to estrogen receptors in humans. They bind to both types of estrogen receptor, Erα receptors and the more recently discovered Erβ receptors.25 Many phytoestrogens seem to have a higher affinity for the Erβ receptor than steroidal estrogens, which suggests that they may exert their actions through distinctly different pathways.26 However, despite their ability to bind to the estrogen receptor, they are much weaker than human estrogens, with 107 to 109 times less activity.26 They seem to possess both estrogenic and antiestrogenic behavior, but whether they act primarily as an estrogen or as an antiestrogen seems to depend on an individual’s amount of circulating endogenous estrogens and the number and type of estrogen receptors.27,28 Even though they have low estrogenic activity, they are frequently present in the body in much higher quantities than endogenously produced estrogens.20 Some have also demonstrated progesterone receptor activity.30

There are 3 main types of phytoestrogens—the isoflavones (the most potent), coumestans, and lignans (Figure). There are more than
1000 types of isoflavones, but the most commonly investigated are genistein and daidzein, which are also thought to have the highest estrogenic properties. They are found in legumes such as soy, chickpeas, clover, lentils, and beans.28 The amount of phytoestrogen found in each soy protein depends on the processing techniques used and its relative abundance in the specific soy product of interest. The secondary soy products (milk or flour) contain lower amounts of isoflavones than the primary products.30 The isoflavones are bound to glucose, and when ingested by humans, are enzymatically cleaved in the gut to the active forms.25 The metabolism of the phytoestrogens varies from person to person, and there is also a sex difference, with women appearing to metabolize them more efficiently.31 The estrogenic activity of the various isoflavones varies greatly. We do not yet know which is the most biologically active form.

The lignans (enterolactone or enterodiol) are found in flaxseed (in huge quantities), lentils, whole grains, beans, fruits, and vegetables.26 Other classes, which are much more rarely ingested, are the coumestans (found in sprouting plants), flavones, flavanones, chalcones, terpenoids, and saponins.

**POTENTIAL BENEFITS OF PHYTOESTROGENS**

Rates of certain diseases, particularly cancers, vary greatly between various geographic regions. In epidemiological observational studies, it was noted that the rates of colon, prostate, and breast cancers were much lower in Japan and other southeast Asian societies than in the United States.32,33 Similar differences were also noted for cardiovascular diseases.34 Interest in the phytoestrogens as therapy for menopausal symptoms began when it was noted that Asian women had approximately 10% the incidence of hot flashes that American women had, but this may be complicated by cultural definitions and beliefs.35,36 These are observational studies with many confounding factors including genetics, psychology, and diet. However, migration studies of Japanese moving to the United States showed the Japanese developed an increased incidence of “Western” disease within 1 or 2 generations.37 Therefore, genetics do not seem to be the only factor and attention has turned to diet. In comparing the Asian diet with that consumed in the West, one of the most significant differences is the high quantity of soy in the Asian diet. The average diet resulted in the ingestion of between 20 and 150 mg/d of soy compared with women in the United States who ingest 1 to 3 mg/d.38

Soy contains high levels of phytoestrogens, particularly the isoflavones. As a result of these observational studies, isoflavones, and particularly soy, are marketed as food supplements and drinks, and also as nonprescription-requiring natural hormone replacement therapy. Is it possible that by supplementing the diet with phytoestrogens that we can improve disease profiles? The evidence is discussed below.

**CANCER PREVENTION**

Phytoestrogens have several potential anticarcinogenic activities. Early studies focused on their estrogenic activity, particularly in their potential ability to reduce the risk of breast cancer, but recent studies have found that their actions are not purely estrogenic, and their nonhormonal activities could be more important in cancer prevention.39 The proposed mechanisms by which they may inhibit cancer cells include the following: (1) inhibition of DNA topoisomerase, (2) suppression of angiogenesis, (3) induction of differentiation in cancer cell lines, and (4) induction of apoptosis.40 Numerous in vitro cell culture studies and in vivo animal experiments have demonstrated that phytoestrogens can inhibit tumors.12 In a comprehensive review on the potential of phytoestrogens to reduce tumor growth, Fournier et al41 noted that 16 of 17 animal studies showed that the addition of soy products reduced tumor incidence or multiplicity in tumor models of the breast, prostate, liver, esophagus, and lung. Isoflavones were the most common soy constituent added (11 studies), but various other components of soy (genistein, soybean saponin, and soy flour) were also used.

Many studies have focused on the isoflavone, genistein, which seems to be the primary anticancer soy constituent. It has antioxidant properties that may also play a role in its anticarcinogenic effects. It can inhibit hydrogen peroxide–induced tumor promoter activity in vitro and in vivo42 and has been shown to inhibit tyrosine kinase.43 Its activity as an anticancer agent probably results from its suppression of enzymes that promote cell growth.

Caution in the interpretation of the available evidence is necessary. Many, but not all, of the tumor-inhibiting effects have been obtained with huge doses of the phytoestrogens, far larger than could be obtained by diet alone. Experimental conditions and isoflavone concentrations varied widely. Cell lines were different and the presence or absence of estradiol also varied. We have no idea what doses and what types of phytoestrogens should be used for tumor suppression, their duration of use, their frequency of use, and the potential or real adverse effects or toxicities. To date, there are no intervention trials using soy or its products in humans for

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**Classification of phytoestrogens.**
primary or secondary prevention of cancer. These studies are needed, but will be difficult to perform and control. In addition, it is difficult to conduct retrospective epidemiological studies on soy intake. Assessments of the amount and types of soy products consumed 3 or 4 decades prior to the study are unreliable, as is the ability to link this information to the development of cancer years later.

No recommendations can be made regarding phytoestrogens’ use in cancer prevention or treatment other than the fact that they seem to have encouraging effects in vitro. Based on this evidence, no conclusive statement can be made about the protective effect of dietary phytoestrogens other than most in vitro and animal studies suggest that the soy constituents, particularly the isoflavones, have antineoplastic activity.

### BREAST CANCER

One of the reasons women are reluctant to take traditional ERT is the fear of developing breast cancer. Recent studies have suggested that the risk of breast cancer in patients receiving ERT increases with the duration of therapy. The magnitude of this association remains controversial, but relative risks are in the range of 1.3 to 2.4 after a minimum of 5 years of therapy.9

Phytoestrogens have structural similarity to estrogens, and it is, therefore, theoretically possible that ingestion could also increase the risk of breast cancer. However, epidemiological studies suggest that phytoestrogen consumption is inversely associated with the development of breast cancer. Countries in which the dietary intake of phytoestrogens is high have some of the world’s lowest incidences of breast cancer.44 These are observational studies only.

Studies on breast cancer and phytoestrogens are summarized in **Table 1**. Early studies looking at the associations of phytoestrogens, particularly genistein, with breast cancer looked at its action on hormone receptors. In one study 48 women who were about to undergo resection of breast masses were given either a daily supplement of isoflavones (45 mg/d) or a placebo for 2 weeks prior to the surgery. The isoflavone-supplemented group had increased growth in the breast lobular epithelium and increased progesterone-receptor expression.45 The significance of this is unknown.

#### Table 1. Summary of Phytoestrogens and Breast Cancer Prevention

<table>
<thead>
<tr>
<th>Source, y</th>
<th>Diet or Intervention</th>
<th>Total Sample Size</th>
<th>Type of Study</th>
<th>Response Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>In Vitro Study</strong></td>
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<tr>
<td>Wang et al,48 1996</td>
<td>Genistein incubated in vitro with human estrogen receptor-positive breast cancer cells</td>
<td>. . .*</td>
<td>Experimental</td>
<td>Low concentrations stimulated growth of breast cancer cells; high concentrations inhibited growth</td>
</tr>
<tr>
<td><strong>Animal Studies</strong></td>
<td></td>
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<tr>
<td>Hsieh et al,47 1998</td>
<td>Mice exposed to mammary carcinogen fed normal diet estrogen supplements, or genistein supplements</td>
<td>. . .</td>
<td>Randomized controlled</td>
<td>Tumors larger in genistein-treated group than in controls</td>
</tr>
<tr>
<td>Lamartiniere et al,103 1995</td>
<td>Rats exposed to genistein and then a mammary carcinogen</td>
<td>. . .</td>
<td>Randomized controlled</td>
<td>Rats exposed to genistein prior to carcinogen had fewer tumors</td>
</tr>
<tr>
<td><strong>Human Studies</strong></td>
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<tr>
<td>McMichael-Phillips et al,49 1998</td>
<td>Daily supplement of isoflavones 45 mg/d or placebo for 2 wk</td>
<td>48</td>
<td>Randomized placebo-controlled</td>
<td>Increased breast lobular epithelial growth and increased progesterone receptor expression compared with placebo</td>
</tr>
<tr>
<td>Ingram et al,53 1997</td>
<td>Urinary excretion of phytoestrogens and breast cancer association</td>
<td>288</td>
<td>Case control</td>
<td>Increased urinary excretion of phytoestrogens associated with decreased breast cancer risk†</td>
</tr>
<tr>
<td>Zheng et al,54 1999</td>
<td>Urinary excretion of isoflavones</td>
<td>120</td>
<td>Case control</td>
<td>Excretion of 5 different isoflavones significantly lower in cases‡</td>
</tr>
</tbody>
</table>

*Ellipsis indicates unknown.
†The odds ratio was 0.27, and the 95% confidence interval was 0.1 to 0.69.
‡P = .04.
vitro, and, like tamoxifen, they have both mild estrogenic and antiestrogenic effects. Therefore, if their antiestrogenic activity is prominent, they could, in theory, reduce the potential carcinogenic effect of prolonged estrogenic activity. 46 Zava and Duwe 46 compared the dose-response to genistein with that of estradiol, tamoxifen, and several other structurally similar iso- and bioflavonoids (equol, kaempferol, and quercetin) in human breast cancer cells in vitro. The results showed that genistein was the only isoflavonoid with potent estrogen agonist and cell growth inhibitory actions over a physiologically obtainable concentration range. The growth-inhibitory action of genistein was distinctly different from those of tamoxifen. 46

However, an experiment done in ovariectomized mice found that genistein actually stimulated mammary cancer growth. 47 The postulated theory was that phytoestrogens, acting as weak estrogens, exhibit estrogenic activity in a low-estrogen environment. These animals, although ovariectomized, were sexually immature. A study by Wang et al 48 investigated the effects of increasing genistein concentrations on estrogen receptor–positive human breast cancer cells. Genistein produced a concentration-dependent effect on their growth. At levels similar to those produced by soy in the diet, DNA synthesis in breast cancer cell lines appeared to be stimulated, 48 but at higher concentrations, genistein inhibited growth. The effects of genistein on growth at lower concentrations appeared to be via the estrogen receptor pathway, while the effects at higher concentrations were independent of the estrogen receptor. It seems as if phytoestrogens could act at other levels in the cell and have the potential, in low concentrations, of inducing breast cancer.

Despite some evidence that genistein has the potential to be a cancer promoter, most in vivo and in vitro studies show that genistein inhibits the growth of breast cancer cells and induces apoptosis in breast cancer cell lines. 49,50 In one study, 51 newborn female rats fed a known mammary carcinogen were randomized to receive supplementary genistein, and there was a 50% reduction in the number of breast cancers in the genistein-exposed group. The timing of genistein administration seemed to be critical in reducing the incidence of breast cancer. Mice fed genistein prior to 35 days of age had a greatly reduced incidence of breast tumors compared with those exposed later in life. 32 Despite encouraging study results in animals, experimental human studies have yet to be performed.

Although there are no experimental human studies, some case-control studies have attempted to link soy intake and breast cancer risk. Most recently, a case-control study of 288 subjects by Ingram et al 53 looked at the association between the urinary excretion of phytoestrogens and breast cancer. Patients were women 30 to 84 years old recently diagnosed as having breast cancer; controls were matched for demographic variables. They found that the increased urinary excretion of some phytoestrogens was associated with a substantial decrease in the risk of breast cancer (odds ratio, 0.27; 95% confidence interval, 0.10-0.69). 53 The amount absorbed is more important than the amount ingested. A study from China of 60 patients with breast cancer showed similar findings, where the median excretion of isoflavones in the patients was 50% to 65% less than in the control subjects. 54 A criticism of this study is the lack of information on a temporal relationship between soy intake and breast cancer development. We do not know if the patients ate diets high in soy before they were diagnosed as having cancer, or whether they had changed their diets over time.

The conflicting results make it difficult to interpret the studies—do phytoestrogens prevent or promote breast cancer growth? It is possible that they demonstrate estrogenic activity in a low-estrogen environment and antiestrogenic activity in a high-estrogen environment. It is, therefore, possible that they have the potential to protect against breast cancer before menopause (high-estrogen environment) and be pro-cancer agents after menopause (low-estrogen environment). This theory is partly supported by a study from Singapore that showed an inverse relationship between soy intake and breast cancer in premenopausal women but not in postmenopausal women. 55 Again, caution in the interpretation of the evidence is necessary. Most of the studies have been conducted in vitro and, owing to conflicting evidence, further research is needed to confirm the action of phytoestrogens. The real worry is that phytoestrogens seem to have the ability to actually promote some breast tumor growth. Further in vitro studies are needed to sort out the conflicting data and, following this, well-designed intervention studies should be performed to confirm whether phytoestrogens can in fact reduce the risk of breast cancer.

CARDIOVASCULAR DISEASE

The incidence of cardiovascular disease increases steeply in women after menopause. Studies have shown that traditional ERT lowers the total serum cholesterol level and increases the high-density lipoprotein cholesterol (HDL-C) level. If used for primary prevention, it is associated with a 35% to 40% decrease in cardiovascular disease mortality. 1,56 These epidemiological data are supported both by clinical trials and basic science research. 2 The “healthy-user” effect has been hypothesized to affect these correlations, but so far, there is no definitive evidence to disprove these large studies.

Because the incidence of cardiovascular disease is lower in countries in which large quantities of soy are consumed in the diet, phytoestrogens, particularly soy, have been investigated as cholesterol-lowering agents since the early 1940s. 2,57 Trials of phytoestrogens in cardiovascular disease prevention are outlined in Table 2. In a large epidemiological study on the relationship between soy product intake and total serum cholesterol concentration, 4838 Japanese men and women had their serum cholesterol levels measured and were interviewed regarding their dietary intake of soy


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Table 2. Summary of Phytoestrogen Supplementation and Cardiovascular Risk Reduction

<table>
<thead>
<tr>
<th>Source, y</th>
<th>Diet or Intervention</th>
<th>Subjects</th>
<th>Total Sample Size</th>
<th>Type of Study</th>
<th>Response</th>
<th>P</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Animal Studies</strong></td>
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<tr>
<td>Anthony et al, 1996</td>
<td>Atherogenic diet, soy protein as protein source vs atherogenic diet no soy</td>
<td>Male and female rhesus monkeys</td>
<td>27</td>
<td>Crossover design 6 mo per diet</td>
<td>LDL-C and VLDL-C levels lowered by 30%–40%, increased HDL-C level (females only)</td>
<td>&lt;.05</td>
<td>Soy diet reduces cardiovascular risk factors in primates receiving an atherogenic diet</td>
</tr>
<tr>
<td>Wagner et al, 1997</td>
<td>4 Diets: (1) animal protein, (2) animal protein + 17β-estradiol, (3) soy isolate, and (4) soy isolate + 17β-estradiol</td>
<td>Ovariectomized female monkeys</td>
<td>48</td>
<td>2 × 2 factorial</td>
<td>Soy protein significantly improved plasma lipid + lipoprotein concentrations</td>
<td>.001 vs .14 soy vs animal fat</td>
<td>Animals receiving soy protein estradiol had least arterial cholesteryl ester content</td>
</tr>
<tr>
<td>Anthony et al, 1997</td>
<td>3 Diets: (1) animal protein, (2) phytoestrogen-depleted soy, and (3) phytoestrogen-containing soy</td>
<td>Male monkeys</td>
<td>82</td>
<td>2 × 2 factorial</td>
<td>Soy with phytoestrogen significantly improved plasma lipid profiles and reduced atherosclerosis by 90%</td>
<td>&lt;.05</td>
<td>Soy-supplemented diet improved cardiac risk factors and reduced atherosclerosis</td>
</tr>
<tr>
<td><strong>Human Studies</strong></td>
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<td></td>
</tr>
<tr>
<td>Nagata et al, 1998</td>
<td>Dietary review of soy intake</td>
<td>Men and women</td>
<td>4838</td>
<td>Cross-sectional</td>
<td>Serum cholesterol measurement</td>
<td>&lt;.001 for trend</td>
<td>There seemed to be a dose response, ie, higher soy intake, lower cholesterol level</td>
</tr>
<tr>
<td>Washburn et al, 1999</td>
<td>3 Diets: (1) comparison diet, (2) 34 mg of phytoestrogen in 1 dose, and (3) 34 mg of phytoestrogen in 2 doses</td>
<td>Postmenopausal women</td>
<td>51</td>
<td>Randomized, double-blind, crossover trial 6 wk on each diet</td>
<td>Soy diet decreased total cholesterol level by 6%, LDL-C by 7%, and systolic blood pressure by 5 mm Hg</td>
<td>&lt;.05</td>
<td>Phytoestrogen supplementation may reduce systolic blood pressure and TC and LDL-C levels</td>
</tr>
<tr>
<td>Wong et al, 1998</td>
<td>2 Diets: (1) NCEP Step I soy protein diet, and (2) NCEP Step I animal protein diet</td>
<td>Men, aged 20-50 y</td>
<td>26</td>
<td>Randomized crossover study diet for 5 wk washout 10 wk</td>
<td>Significant LDL-C and LDL/HDL ratio decreases</td>
<td>.03 for LDL-C and .05 for LDL/HDL ratio</td>
<td>Soy protein diet reduced LDL-C level and LDL/HDL ratio and response was independent of original cholesterol level</td>
</tr>
<tr>
<td>Cassidy et al, 1994</td>
<td>2 Diets: 45 mg/d or 23 mg/d of isoflavonoids</td>
<td>Premenopausal women</td>
<td>15</td>
<td>Crossover trial 4-5 wk on each diet</td>
<td>45-mg/d dose associated with a significant drop in TC and LDL-C levels</td>
<td>&lt;.05</td>
<td>Isoflavonoid supplementation reduced TC and LDL-C levels in premenopausal women</td>
</tr>
<tr>
<td>Nestel et al, 1997</td>
<td>40 mg/d of genistein (in pill form)</td>
<td>Women</td>
<td>15</td>
<td>Placebo-controlled crossover 10-wk trial</td>
<td>No significant change in LDL-C level and arterial compliance improved 26%</td>
<td>&gt;.05 and &lt;.001</td>
<td>Genistein supplements did not improve lipid profile but did improve arterial compliance</td>
</tr>
<tr>
<td>Hodgson et al, 1998</td>
<td>55 mg/d of isoflavonoids (in pill form) with subjects normal diet</td>
<td>Men and women with normal cholesterol levels</td>
<td>46 men and 13 women</td>
<td>Randomized, double-blind, placebo-controlled, 2-way parallel design</td>
<td>No significant difference in cholesterol levels</td>
<td>&gt;.05</td>
<td>Patients with normal cholesterol levels do not seem to benefit from isoflavone supplementation</td>
</tr>
</tbody>
</table>

* LDL-C indicates low-density lipoprotein cholesterol; VLDL-C, very low-density lipoprotein cholesterol; TC, total serum cholesterol; and NCEP, National Cholesterol Education Panel.
and soy products. A significant trend ($P<.001$) was observed for decreasing total serum cholesterol concentration with an increasing intake of soy products in both men and women suggesting a dose-response relationship. However, it is also possible that persons who use soy as a protein source may have a lower intake of animal proteins and, therefore, a concomitant reduction in cholesterol and saturated fat intake.

There are several mechanisms by which dietary phytoestrogens could prevent or reduce atherosclerosis including antioxidant activity, improvement in plasma lipid concentrations, reduction of thrombus formation, and improvement in vascular compliance. The mechanisms by which they could improve plasma lipid profiles are poorly understood. Proposed mechanisms of action include the following: increased bile acid secretion, direct action on estrogen receptors, inhibition of endogenous cholesterol synthesis, up-regulation of the cholesterol receptors, and enhanced thyroid function (an elevated thyroxine level reduces the cholesterol level). Studies investigating the potential cardioprotective effects of phytoestrogens have been done on both primate and human subjects. In 1996, Anthony et al studied 27 peripubertal male and female rhesus monkeys fed moderately atherogenic diets with soy protein as the protein source. In a cross-over design, the monkeys were fed a phytoestrogen-depleted soy protein for 6 months and a phytoestrogen-containing soy protein for 6 months. The phytoestrogen diet significantly decreased the low-density lipoprotein cholesterol (LDL-C) and very low-density lipoprotein cholesterol levels in both male and female monkeys by 30% to 40% and increased the HDL-C level by 15% in females. In addition, the total serum cholesterol level–HDL-C ratio decreased by 20% in the male monkeys and 50% in the female monkeys. A similar study was conducted in 1997 on ovariectomized female monkeys fed 1 of the following 4 diets: animal protein (casein) alone, animal protein with 17β-estradiol, soy isolate alone (which contained soy phytoestrogens), or soy isolate with 17β-estradiol. Soy protein improved the plasma lipid profiles, and soy protein combined with estradiol improved the lipid profiles even further. In one further study by Anthony et al young male cynomolgous monkeys were fed 1 of the following 3 diets for 14 months: animal protein, phytoestrogen-depleted soy, or phytoestrogen-containing soy. Again, those fed phytoestrogen-containing soy had improved lipid profiles compared with the other 2 groups. In addition, autopsy studies done on a random sample of each group showed that the group fed phytoestrogens had 90% less atherosclerosis than those fed animal protein.

There are numerous small sample size studies on human looking at the potential cardiovascular benefits of phytoestrogens. In an attempt to combine these, Anderson et al performed a meta-analysis of 38 controlled trials of soy protein use for cholesterol reduction in humans. Thirty-four of 38 studies showed an improvement in lipid values. Overall, an average of 47 g of soy protein intake per day resulted in statistically significant reductions of 9.3% in the total serum cholesterol level, 12.9% in LDL level, and 10.5% in triglyceride levels. There was no overall change noted in HDL-C or very low-density lipoprotein levels. In addition, the higher the patient’s initial total serum cholesterol level, the better their response to soy intake. Those with normal cholesterol levels with initial cholesterol values below 5.2 mmol/L (<200 mg/dL) had nonsignificant decreases of 4.4%, whereas subjects with initial values above 8.66 mmol/L (≥335 mg/dL) had significant reductions of 19.6%. There was insufficient data to analyze the effects based on sex.

Since 1995, further small human studies have been conducted. Washburn et al carried out a randomized, double-blind, crossover trial in 51 perimenopausal women. Subjects received the following 3 diets in sequence, each given for 6 weeks: a comparison carbohydrate-based diet; a diet with 34 mg of supplemental phytoestrogens in a single dose; and a diet with 34 mg of phytoestrogens split in 2 doses. Significant declines in total serum cholesterol (6%) and LDL-C (7%) levels were noted in the 2 groups receiving the soy diets as compared with the group receiving the carbohydrate diet. A significant decrease of 5 mm Hg in systolic blood pressure was also noted in the subjects receiving twice daily soy supplements compared with the carbohydrate only diet. To establish whether soy protein lowered the total cholesterol level in normocholesterolemic subjects on a National Cholesterol Education Panel Step I diet, Wong et al conducted a randomized crossover study. Thirteen normocholesterolemic and 13 hypercholesterolemic men aged between 20 and 50 years were fed either a National Cholesterol Education Panel Step I soy protein diet or an National Cholesterol Education Panel Step I animal protein diet for 5 weeks, followed by a washout period of 10 to 15 weeks, and then the alternate diet for 5 weeks. The hypocholesterolemic effect of soy protein was found to be independent of age and body weight. Regardless of original lipid status, the soy protein diet was associated with a statistically significant decrease in the plasma concentrations of LDL-C ($P=.03$) and the ratio of plasma LDL-C to HDL-C ($P=.005$).

Following from the primate studies, interest has centered on finding the component of soy that is most responsible for its cholesterol-lowering ability, primarily the isoflavones—genistein and daidzein. In 15 healthy young women with normal cholesterol levels, it was found that 45 mg/d of isoflavonoids, but not 23 mg/d, resulted in a significant decrease in total serum cholesterol and LDL-C levels. In a noncontrolled trial Nestel et al studied 15 perimenopausal and postmenopausal women fed 45 mg/d of genistein over 10 weeks. Although there was no significant change in LDL-C levels after treatment, arterial compliance improved by 26%, a similar degree to that encountered in women who receive conventional ERT. Not all trials have shown an improvement in lipid profiles. Hodgson et al looked at 46 men and 13 postmenopausal women.
who were given 55 mg/d of isoflavonoids (mainly genistein) in pill form over 8 weeks in a 2-way parallel design. There was no difference noted in baseline and posttreatment cholesterol levels and it was concluded in this study that patients with normal cholesterol levels at baseline do not have a significant improvement when fed isoflavonoids.

Variability in study design (particularly the type and amount of phytoestrogen used); study subjects (age and sex varies greatly); and outcomes studied make the studies done on cholesterol lowering associated with phytoestrogens hard to synthesize. The numbers of subjects studied are generally small (usually <100, often <30). It seems as if the beneficial effects are greater in those with elevated, rather than normal, cholesterol levels. Overall, phytoestrogen supplementation seems to have a beneficial effect on lipid values, but the magnitude of that effect, its clinical significance, and the amount of soy isoflavones required to obtain it are still in question. Despite the inconsistencies, there are no studies to date showing an elevation of lipid values with the use of these diets.

Is there other evidence for improvement in cardiovascular disease? Although soy protein may reduce the lipid values, there are no studies to date studying the long-term effects of soy in coronary heart disease prevention. There is strong epidemiological evidence that the risk of heart disease in Asian countries is significantly lower than the United States, but this is confounded by the fact that the Asian diet also has low saturated fat.76 There is only one primate study that shows that a diet high in soy reduced atherosclerosis, which could affect the rate of heart disease.77 There is also interest in the platelet inhibitory function of genistein in vitro. Nakashima et al78 showed that platelets incubated in vitro with genistein completely inhibited platelet aggregation induced by thromboxane A2 and collagen analogues.78 The mechanisms by which this occurs are poorly understood, and the clinical significance and application of this requires further study. Additional studies are needed to look at the effect of isoflavones and other phytoestrogens on lipoproteins, hemostasis, and vascular function.

**HOT FLASHES OR MENOPAUSAL SYMPTOMS**

Hot flashes are prevalent at menopause and are the most common reason cited by menopausal women for starting ERT. Their prevalence varies greatly with geographic distribution from 70% to 80% of women in the United States to 10% to 14% in Singapore and Japan.36,79 Interestingly, it appears that ERT does not seem to reduce the incidence of menopausal hot flashes in Asian women. Chung et al80 carried out a double-blind study on 83 Hong Kong Chinese women with a surgical menopause randomized to receive treatment with 0.625 mg/d of estradiol. There was a significant increase in the serum estradiol concentration with treatment compared with placebo (P<.001) but no significant difference in the frequency of hot flashes between the groups. It was hypothesized that the dietary intake of phytoestrogens could have negated the effects of estradiol on menopausal symptoms, but actual dietary habits of the subjects were not recorded in this study.

Few controlled studies have been done looking at the effects of phytoestrogens on menopausal symptoms (Table 3). Washburn et al73 noted a statistically significant decrease in vasomotor symptoms and hypoestrogenic symptoms in 51 patients fed phytoestrogen supplements (17 mg) twice daily compared with patients receiving placebo. However, this supplement did not improve other menopausal symptoms, such as mood swings, and did not affect the overall quality of life.73 Albertazzi et al81 looked at the effect of daily dietary supplementation of soy protein isolate powder on hot flashes in 104 postmenopausal women in a 12-week, double-blind, parallel, randomized placebo-controlled trial. Patients were assigned to either 60 g/d of isolated soy protein or 60 g/d of placebo (casein). By the end of the 12th week, patients taking soy had a 45% reduction in their daily hot flashes vs a 30% reduction obtained with placebo (P<.01). Murkies et al82 randomized 58 postmenopausal women in a double-blind study design. Patients received either a supplement of wheat or soy flour (45 g/d) over 12 weeks. Overall, those receiving soy flour had a reduction of 40% in the frequency of hot flashes compared with a reduction of 25% in those receiving wheat flour. Although both studies had statistically significant results, the clinical

<table>
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<th>Source, y</th>
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<tr>
<td>Washburn et al, 1999</td>
<td>Phytoestrogen supplement, 17 mg twice daily</td>
<td>51</td>
<td>Placebo-controlled trial</td>
<td>Significantly reduced vasomotor and hypoestrogenic symptoms</td>
<td>&lt;.05</td>
<td>Reduced hot flashes, but no change in mood swings or quality of life</td>
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<tr>
<td>Albertazzi et al, 1998</td>
<td>Phytoestrogen, 60 g/d, for 12 wk</td>
<td>104</td>
<td>Randomized, double-blind, placebo-controlled</td>
<td>45% Reduction in hot flashes compared with 30% for placebo</td>
<td>&lt;.01</td>
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<td>Murkies et al, 1995</td>
<td>Wheat or soy flour, 45 g/d</td>
<td>58</td>
<td>Randomized double-blind</td>
<td>Soy flour reduced hot flashes by 40% or wheat flour, by 25%</td>
<td>&lt;.001</td>
<td>Statistically significant reduction of hot flashes</td>
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significance is unclear. A 15% reduction in hot flashes would mean a reduction of 1 hot flash per day in patients experiencing 10 or 12 hot flashes per day. This would be of limited practical benefit.

OSTEOPOROSIS

Estrogen replacement therapy is highly effective at reducing the rate of bone loss and can also replace lost bone. Epidemiological data suggest that osteoporosis is about one third as common in Japanese women (who consume a diet rich in soy products) compared with those consuming a Western diet. The extent to which this is genetic is unknown.

To date, few controlled trials have been done specifically looking at phytoestrogens and osteoporosis in women. Kardinaal et al in the Netherlands hypothesized that the rate of bone loss is inversely associated with urinary excretion of phytoestrogens used as a surrogate marker of dietary intake. They compared the excretion of flavonoids in the urine of 35 women who had a high rate of bone loss (2.5% per year) with the excretion of flavonoids in 35 women with a low rate of bone loss (<0.5% per year). There was no difference in the excretion of isoflavonoids between the 2 groups and it was concluded that there did not seem to be a protective effect. However, animal models have demonstrated possible positive effects of isoflavones on bone. It has been shown recently in a placebo-controlled trial that ovariectomized rats fed a diet of genistein had a significant decrease in bone loss.

All phytoestrogens are unlikely to be the same when it comes to osteoporosis prevention. Interest is centered on ipriflavone in the prevention of bone loss. It is a synthetic nonhormonal drug produced commercially from the isoflavone daidzein. Ipriflavone does not seem to act through direct estrogen receptor activity and, therefore, is not strictly a phytoestrogen. However, approximately 10% of the ingested dose is converted back to daidzein in the body. Its lack of estrogenic properties was investigated in a study of 15 postmenopausal women given ipriflavone treatment. The levels of follicle-stimulating hormone, luteinizing hormone, prolactin, and estradiol did not change following administration of 600 mg/d and 1000 mg/d to 2 groups of women, even after 21 days of treatment. In addition, there was no change in vaginal cytology after 21 days of treatment. To date, this apparent lack of hormonal activity has not been investigated using higher doses of ipriflavone. Most of the studies about ipriflavone efficacy have been done in Italy, Hungary, and Japan. Ipriflavone has been shown to inhibit bone resorption by mouse osteoclasts and to inhibit parathyroid hormone activity. It has been shown that the 5 metabolites of ipriflavone can increase alkaline phosphatase activity and collagen formation in vitro.

Several double-blind human studies have shown a beneficial effect of ipriflavone in reducing bone loss. In 1997 Gambacciani et al observed the effect of ipriflavone combined with ERT in postmenopausal women. The study consisted of 4 groups of postmenopausal women treated for 2 years with one of the following: (1) only a calcium supplementation (500 mg/d), (2) ipriflavone (600 mg/d) plus the same calcium dose, (3) low-dose conjugated estrogens (0.3 mg/d) plus calcium, or (4) low-dose ipriflavone (400 mg/d) plus low-dose conjugated estrogens plus calcium. The most beneficial effects in reducing bone loss were seen in patients who received the low-dose ipriflavone with estrogens and the ipriflavone with calcium with a significant (P < .05) increase in vertebral bone density seen in these groups. In another placebo-controlled study, 98 women with an established diagnosis of osteoporosis were given ipriflavone, 200 mg, 3 times daily. After 2 years of treatment, the placebo-treated group had lost 3.5% of bone mass, but those treated with ipriflavone had maintained or slightly increased their bone density. A further placebo-controlled study with 453 participants and the same study design also showed similar results after 2 years.

There is some evidence that, in addition to slowing bone loss, ipriflavone treatment can increase bone mass. In a 1-year, double-blind, placebo-controlled, parallel group clinical trial, 41 postmenopausal women received ipriflavone and 50 received placebo. Six months later the ipriflavone-treated group had a statistically significant increase in vertebral bone mineral density, whereas it decreased in the placebo-treated group. In a smaller Italian study, 28 women older than 65 years, having a diagnosis of osteoporosis and radiographic evidence of at least one vertebral fracture, were treated with ipriflavone (600 mg/d) or placebo in a randomized, double-blind, parallel group design. All patients received 1000 mg/d of calcium. After 12 months there was a 6% increase in bone mineral density at the distal radius in the ipriflavone-treated group (P < .05). Bone mineral density values did not change in the placebo group.

In general, ipriflavone seems safe. However, most studies look at its use over a 2-year period only. Because it seems to have no estrogenic effects, ipriflavone may be less likely to increase the risk of estrogen-dependent cancers but it is also unlikely to help prevent cardiovascular disease. Caution is urged in the interpretation of these studies, as ipriflavone is synthetic, and not a naturally occurring substance, and the amount of ipriflavone per pill is far higher than any amount that could be obtained from dietary phytoestrogens. Whether dietary phytoestrogens could have the same or similar effects remains to be seen. In vitro studies are being conducted on the effects of daidzein and genistein on bone growth, but there are no human studies available.

ADVERSE EFFECTS

Although the evidence is increasing that there may be some benefits to the addition of soy and soy products to the diet, there are many questions left unanswered. One of the most important is the potential adverse effects. The potential for inducing breast cancer growth in a low-estrogen environment needs to be investigated further. Use of phytoestrogens has also been found to affect concentrations of thyroxine, insulin, and glucagon.

(Reprinted) Arch Intern Med/Vol 161, May 14, 2001 WWW.ARCHINTERNMED.COM 1169

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fore, they have the potential to act as endocrine disrupters. Evidence from animal studies suggests that ingestion of larger quantities of phytoestrogens can adversely affect fertility. Original studies done on phytoestrogens involved some studies where sheep, exposed to high levels of clover in their fodder, became infertile.99 Rats fed a diet high in coumestrol maintained a state of chronic anovulation.100 Six premenopausal women fed soy milk daily for 1 month had significantly decreased levels of estradiol, which persisted for 2 to 3 months after stopping the intervention.101 The menstrual cycle length also increased by about 4 days in the patients fed soy, although there was no statistical significance possibly owing to the small size of the study. Despite these concerns, there is no definitive evidence that the consumption of phytoestrogens at the levels normally encountered in the diet is likely to be harmful in adults.

SUMMARY

Interest in the use of phytoestrogens as an alternative to traditional ERT has increased tremendously over the past 3 to 5 years owing to the popular perception that they could be a natural alternative to prescription medication. Most evidence on the benefits of phytoestrogens comes from in vitro and animal studies. Little research has been done in humans, and the current epidemiological evidence could be confounded by many factors. Without human data, little can be extrapolated to the potential effects in humans.

Although evidence of the beneficial effects of phytoestrogens is increasing, current evidence for the benefits of taking traditional ERT is far more convincing than that for phytoestrogen consumption. There is epidemiological and in vitro evidence, but no human clinical trials, linking phytoestrogen ingestion to the lower rates of certain cancers. However, the specific dietary elements that provide cancer protection have not been elucidated. In addition the temporal relationships of phytoestrogens and cancer protection have yet to be established, and these may be important. For example, it seems that developing breast tissue responds most to phytoestrogens. Animal studies suggest that the cholesterol level is lowered by increased phytoestrogen intake and there is also some evidence from human studies to suggest that phytoestrogens may reduce cholesterol levels in persons with preexisting hypercholesterolemia. Evidence is weak for the phytoestrogens’ ability to reduce menopausal symptoms. Ipriflavone, a synthetic isoflavone, may be helpful for osteoporosis prevention.

What doses and what types of phytoestrogens are best? Current evidence is too preliminary to even suggest doses that may have the maximum benefit. Even if patients switch to soy products, several factors affect the bioavailability. Xu et al102,103 found that daidzein is more bioavailable than genistein. The efficacy can vary considerably based on the type of gut microflora present.104 The doses may vary considerably depending on whether the aim is cancer prevention or prevention of menopausal symptoms. Are there particular phytoestrogens that protect or treat certain diseases? Do these effects increase as dose increases? Could the unopposed estrogens from phytoestrogens actually produce cancers in persons who are susceptible? What are needed are prospective randomized controlled trials, particularly to observe the effect on vascular tissue, breast tissue, and endometrium.

It is a simplistic view that by adopting the diet of another country one can automatically assume the disease profile of that country. Multiple confounders make this premise unlikely. Phytoestrogens consumed alone may not be helpful, but may require combination with other dietary elements to exert their effects. Their beneficial effects could also be unique to Asian populations and not work so well in Western populations because of genetic differences. In addition, changing disease profiles does not mean an increase in longevity. Japan has a life expectancy greater than that of the United States, but Mediterranean countries, such as Italy, have a better life expectancy than Japan. Safety of phytoestrogens is also a concern. Although these substances are consumed in large quantities in certain countries and, therefore, dietary phytoestrogen consumption appears to be “safe,” we do not know their effects when taken long-term or in high doses such as those found in supplements. Phytoestrogens’ estrogenic activity could potentially result in the problems seen with unopposed estrogens, including an elevated risk of endometrial and breast cancer. This risk could theoretically increase with ingestion of larger quantities.

CONCLUSIONS

Recommending replacement of ERT with soy-based or plant-based phytoestrogens is premature. Current evidence does not permit us to draw firm conclusions owing to small sample sizes, frequent lack of control and placebo groups, variability of study designs, and huge variations in the amount and types of phytoestrogens used. Evidence for the beneficial effects of phytoestrogens is increasing, but further studies are needed. There is insufficient evidence to recommend specific quantities or types of phytoestrogens for the prevention or the treatment of any diseases. The most prudent recommendation is to eat a diet high in fruit, vegetables, and fiber, and low in meat and saturated fat content. This is consistent with current recommendations and would increase overall dietary phytoestrogen intake. Further recommendations cannot be made.

Accepted for publication November 7, 2000.

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