Coronary artery disease is the leading overall cause of mortality for women and increases dramatically after menopause. Estrogen has many beneficial cardiovascular actions although concerns have been raised about its effects on the progression of breast and uterine neoplasms and its tendency to increase coagulability. Selective estrogen agonists may be superior to conventional estrogens. A dietary source of a partial estrogen agonist is the plant-based group of phytoestrogens, which include isoflavones, lignans and coumestans. Phytoestrogens have a similar structure to estradiol and have weak affinity for the estrogen receptor. Epidemiologic data indicate that women ingesting high amounts of phytoestrogens, particularly as isoflavones in soy products, have less cardiovascular disease, breast and uterine cancer and menopausal symptoms than those eating Western diets. Preclinical and clinical studies have found that isoflavones have lipid-lowering effects as well as the ability to inhibit low-density lipoprotein oxidation. They have been shown to normalize vascular reactivity in estrogen-deprived primates. Furthermore, phytoestrogens have antineoplastic effects with inhibition of cellular proliferation as well as angiogenesis, properties that could be protective against cancer development. Finally, menopausal symptoms and bone density may be favorably influenced by phytoestrogens. In summary, phytoestrogens, in the form of dietary isoflavones, represent a new area to explore in pursuit of nutritional approaches to cardiovascular protection. (J Am Coll Cardiol 2000;35:1403–10) © 2000 by the American College of Cardiology
modest, but nevertheless concerning, increased incidence of breast cancer in women taking estrogens is a major limitation of this prophylactic therapy (14). Angiogenesis, a fundamental process necessary for tumorigenesis as well as atherosclerotic progression, can be enhanced by estrogen (15), which induces expression of cellular adhesion molecules and organization of endothelial cells into primitive blood vessels, upon which tumors depend. The effect of estrogen upon the coagulation system is variable. Platelets incubated with estradiol manifest decreased adherence (16) and aggregation (17) although studies in women on HRT have not shown similar antiplatelet effects (18,19). Other reports have noted decreased fibrinogen (4) and decreased plasminogen activator inhibitor (20–22) levels in women taking HRT, which may be protective, although thrombotic events are actually increased in this population (13).

**PHYTOESTROGENS: AN ALTERNATIVE TO ESTROGEN?**

Given the demonstrated risks to conventional HRT, many women and their practitioners have been in search of alternatives. Phytoestrogens are naturally occurring estrogens that may have beneficial effects on the cardiovascular system and may also alleviate common illnesses afflicting women, such as menopausal symptoms, osteoporosis and breast cancer (Table 1). Phytoestrogens may have advantages over conventional estrogens in that they may lower LDL cholesterol without inducing hypertriglyceridemia (23); they may relieve menopausal symptoms without increasing the risk of uterine or breast neoplasia (24); they may enhance vascular function without accelerating pathological angiogenesis (25); and there are no reports of increased thrombotic events. There is not yet enough evidence from large randomized clinical trials to make an unqualified recommendation about the use of phytoestrogens, but accumulating data indicate that phytoestrogens may be an alternative therapy for postmenopausal women at risk for CVD. The evidence for cardiovascular benefit of phytoestrogens is the subject of this review.

**PHARMACOLOGY AND PHYSIOLOGY OF PHYTOESTROGENS**

Phytoestrogens are naturally occurring, plant based diphenolic compounds that are similar in structure and function to estradiol (Fig. 1). There are many types of phytoestrogens, but the major categories include isoflavones, lignans and coumestans. Common and significant sources of phytoestrogens are soybeans (isoflavones), cereals and oilseeds such as flaxseed (lignans) and alfalfa sprouts (coumestans). These estrogen-like compounds were identified in the 1940s, when an epidemic of infertility among sheep was investigated. The animals were grazing on clover (Trifolium sp)—a plant with a high content of formononetin, which is converted by ruminal bacteria to isoflavones, the predominant type of phytoestrogens.

**Table 1. Effects of Phytoestrogens in Basic, Animal and Human Studies**

<table>
<thead>
<tr>
<th>Preclinical Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol (44,45,50)</td>
</tr>
<tr>
<td>LDL oxidation (46)</td>
</tr>
<tr>
<td>Antioxidant enzymes (48)</td>
</tr>
<tr>
<td>Atherosclerotic lesions (45)</td>
</tr>
<tr>
<td>Vascular reactivity (54,55)</td>
</tr>
<tr>
<td>Platelet aggregation (51,52)</td>
</tr>
<tr>
<td>Expression of ICAM-1 and VCAM-1 (49)</td>
</tr>
<tr>
<td>Angiogenesis (25,61)</td>
</tr>
<tr>
<td>Neoplastic proliferation (62–66,68)</td>
</tr>
<tr>
<td>Bone loss (88,89)</td>
</tr>
</tbody>
</table>

**Clinical Studies**

<table>
<thead>
<tr>
<th>Beneficial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol (23,41,42)</td>
</tr>
<tr>
<td>LDL oxidation (47)</td>
</tr>
<tr>
<td>Perimenopausal hot flashes (56)</td>
</tr>
<tr>
<td>Cancer incidence (69,73–84)</td>
</tr>
<tr>
<td>Bone mineral density (90)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Detrimental</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast secretions (85)</td>
</tr>
<tr>
<td>Proliferation of breast epithelium (86)</td>
</tr>
</tbody>
</table>

*See text for details. ICAM-1 = intercellular adhesion molecule; VCAM-1 = vascular cell adhesion molecule.
The most common and best studied phytoestrogen is the class of isoflavones. The most abundant active components of isoflavones are genistein and daidzein. These agents appear to have selective estrogenic actions, i.e., in some tissues they display prooestrogenic responses, whereas in others, they inhibit estrogenic effects. The recent identification of a second subtype of estrogen receptor lends support to the theory of selective estrogenic action (26,27). Estrogenic activity is dependent on the affinity of binding to the estrogen receptors, which is determined by the presence of the aromatic ring as well as hydroxyl groups at specific sites (28). Compared with estradiol, genistein and daidzein bind estrogen receptors with 100 and 1,000 times less affinity, respectively (29). Nevertheless, in the quantities that can be consumed in the diet, isoflavones can have biological effects. Antiestrogenic effects may be due to competitive inhibition at the estrogen receptor, interference with gonadotrophins, inhibition of estrogen synthesis or increased synthesis of estrogen-binding protein. Phytoestrogens do not have feminizing effects in male primates as reflected by unchanged weights of the reproductive organs in these animals, although prenatal exposure of rats resulted in diminished weights of ovaries and uteri in females (30).

Isoflavones are widely consumed by Asian populations, predominantly in the form of soy. The typical concentration of genistein in soy foods is 1 to 2 mg per g of protein, and Asians consume 20 to 80 mg of genistein per day in the usual diet. By contrast, the average American ingests only 1 to 3 mg per day (31). Dietary studies can be inconsistent, however, as there is significant variation of isoflavone content between varieties of soy beans, the particular crop, as well as the processing methods. Isoflavones are inactive molecules when in the form of glycosides (genistin, daidzein), but as aglycones (genistein, daidzein) intestinal absorption is possible. Intestinal absorption varies greatly between individuals, which may be related to the content of dietary fiber and the state of intestinal microflora. After absorption, isoflavones are reconjugated to glucuronides and excreted unchanged in the urine (32). Plasma levels increase 6 1/2 h after ingestion in a dose dependent fashion (33), and urinary levels increase dramatically after supplemented diets have begun. For example, urinary levels of genistein increased from 0.8 umol/day to 26 umol/day and daidzein from 0.3 umol/day to 23 umol/day after a nine day ingestion of 100 g tofu and 45 g soy protein isolate (34).

Concentrations of the phytoestrogens and their metabolites can be measured in urine, plasma and other bodily fluids and vary widely, even during controlled nutrition studies. As dietary phytoestrogen metabolism is profoundly influenced by gastrointestinal flora, antibiotic use or bowel disease will modify metabolism and therefore, bioavailability. Equol is a metabolite of daidzein, which shows enormous variation in urinary excretion. Some studies have distinguished individuals as either equol excreters or non-excreters because the excretion rates vary so substantially (35). However, this appears to be independent of the dose-dependent excretion of genistein and daidzein. Chronic ingestion of isoflavones also affects their metabolism. For example, after one month of a high soy diet (36 oz of soymilk containing 100 mg daidzein and 115 mg genistein), young, healthy women exhibit increased absorption rates, as indicated by a higher peak serum level, but also accelerated excretion based on the percentage of ingested isoflavone recovered in the urine (36).

There are many other natural agents classified as phytoestrogens, based on their structure or function. Resveratrol is another potentially important phytoestrogen with a structure similar to diethylstilbestrol. Resveratrol is present in grapes and, therefore, wine and has been proposed to be the agent responsible for the “French-paradox” (37). The French paradox derives from the epidemiological observation that the French and Italian populations suffer from less CVD than other Europeans and Americans, despite a relatively high intake of dietary fat. Resveratrol has been shown to bind to human estrogen receptors, initiate transcriptional activity dependent on the estrogen-response element, activate estrogen-regulated genes, cause proliferation of estrogen-dependent breast cancer cell lines and inhibit the expression of vascular cell adhesion molecule-1 (VCAM–1) and intercellular adhesion molecule-1 (ICAM–1) in human endothelial cells (38). Its action can also be inhibited by estrogen antagonists such as tamoxifen (39).

**BENEFICIAL CARDIOVASCULAR EFFECTS**

Favorable effects of phytoestrogens on lipid profiles, vascular reactivity, thrombosis and cellular proliferation have been reported. It is plausible that the lower incidence of CAD in populations ingesting diets high in phytoestrogen is due to an improved lipid profile. In a study of 24 healthy normocholesterolemic men assigned to either a low fat soy diet or low fat animal protein diet, no difference was observed in total cholesterol levels (40), but when patients with type II hyperlipoproteinemia (mean TC 409 mg/dL) were placed on high soy diets for four weeks, the total cholesterol and LDL decreased by 16%. These changes were attributed to increased LDL degradation (41). A later study designed specifically to examine diets differing only in their protein source randomly assigned healthy men to diets either: 1) high in fat, 2) low in fat with soy protein, or 3) low in fat with animal protein. Both of the low fat diets decreased total cholesterol levels and blood pressure compared with the high fat diet, but the soy protein had a more potent hypocholesterolemic effect (10% vs. 5% decline in total cholesterol) (42).

Although some published studies have failed to observe a fall in cholesterol values on a soy-based diet, a meta-analysis of 38 trials of soy protein consumption in humans revealed an improvement in total cholesterol by 9% and LDL by 13%, as well as a decrease in triglyceride levels of 10% (23). In these trials, the average intake of soy was 47 g/day. The
extent of reduction was dependent upon the baseline level of cholesterol; for example, in subjects with moderate hypercholesterolemia (259–333 mg/dL), a decrease in total cholesterol of 7.4% was observed, whereas subjects with severe hypercholesterolemia (>335 mg/dL) achieved a decline of 19.6%.

Three theories of possible mechanisms for the hypocholesterolemic effects of phytoestrogens have been proposed. One explanation is that phytoestrogens cause an increase in the excretion of bile acids and, therefore, enhance removal of LDL. Others have proposed that phytoestrogens initiate a hyperthyroid state, supported by the finding in some studies of increased free thyroxine levels after feeding soy proteins to animals (43). The third and best supported mechanism of phytoestrogen lipid-lowering is that of altered hepatic metabolism with augmented LDL and VLDL removal by hepatocytes. Sirtori et al. (44) demonstrated substantial reductions in cholesterol levels with enhanced LDL degradation and increased binding of radiolabeled LDL to receptors. A study using the LDL-receptor deficient mouse has provided further support for an effect of isoflavones on LDL receptor activity (45). When normocholesterolemic C57BL/6J mice were fed a high cholesterol, isoflavone-poor diet, they developed hyperlipidemia and intimal lesions in the proximal aorta. However, those animals fed an isoflavone-rich diet exhibited a decrease in total cholesterol and VLDL cholesterol. By contrast, this benefit of an isoflavone-rich diet was not observed in LDL-r null mice, suggesting that isoflavones may reduce lipid levels by increasing the activity of the LDL receptor. Furthermore, there was a 50% reduction in intimal lesion area in isoflavone treated C57BL/6J but not LDL-r null mice, again implicating an effect of isoflavones on LDL receptor activity in conferring cardiovascular protection.

Isoflavones may also inhibit oxidation of LDL. Kapisot and colleagues (46) observed that LDL oxidation products, assayed as Thiobarbituric Acid–Reactive Substances in either cell free or endothelial cell systems, were strongly inhibited by genistin, somewhat inhibited by daidzein but not affected by genistein (the glycosylated form of genistein) or control. Furthermore, both genistein and daidzein were found to protect against cytotoxic effects of oxidized LDL as assessed by cellular morphologic features and lactate dehydrogenase release by cultured endothelial cells. A trial in humans enrolling healthy volunteers consuming three soy bars per day for two weeks (total 36 mg genistein and 21 mg daidzein per day) demonstrated a significant amount of genistein and daidzein within the LDL fractions, as well as a significant prolongation of the lag time to LDL oxidation, implying an antioxidant effect (47). Genistein has also been shown to inhibit hydrogen peroxide production and increase the activity of antioxidant enzymes, such as catalase, superoxide dismutase, glutathione peroxidase and glutathione reductase. Furthermore, genistein, and to a lesser degree daidzein, can inhibit superoxide anion generation by xanthine/xanthine oxidase (48).

Atherosclerosis is initiated by monocytes binding to the endothelium and migrating into the intimal layer to develop into foam cells. The adhesiveness of endothelial cells is due to lipid-induced, oxidant-sensitive transcription of adhesion molecules and chemokines, which promote monocyte binding. This binding is reliant upon intercellular signalling and oxidant-sensitive transcription of adhesion molecules. Phytoestrogens may further protect against atherosclerosis by interfering with these initial processes. Although scant information has been published thus far, genistein is capable of inhibiting the expression of ICAM-1 and VCAM-1 on human endothelial cells co-cultured with monocytes (49). Furthermore, by reducing oxidative stress, it is possible that phytoestrogens deactivate the transcriptional pathways leading to the expression of genes involved in monocyte adhesion and infiltration.

The response to isoflavones is influenced by gender. Monkeys that were fed an atherogenic diet followed by a soy protein phytoestrogen-rich diet in a six-month crossover trial had a lowering of LDL and VLDL levels compared with control values. However, female animals additionally manifested an increase in HDL, decrease of lipoprotein (a), lower LDL molecular weight, decrease in apolipoprotein B, A1, A2 and no hypertriglyceridemia (50).

Phytoestrogens may have less prothrombotic tendencies than the currently used formulations of estrogen. In vitro studies of genistein and daidzein reveal decreased platelet aggregation by collagen and thromboxane (51,52), which may be due to an inhibition of binding of the thromboxane receptor or diminished tyrosine phosphorylation. However, in a small study of 20 healthy, normocholesterolemic men fed a soy diet for 28 days, a significant increase in plasma levels of genistein and daidzein occurred but without a change in platelet aggregation (53). It was suggested that on such supplements, serum levels of the active compound do not reach levels comparable with those required to affect platelet aggregation in the in vitro studies.

Preclinical studies suggest that vascular reactivity may be favorably influenced by phytoestrogens. Primates manifest an improvement in endothelium mediated vasodilation when treated with phytoestrogens. Specifically, postmenopausal monkeys on a phytoestrogen-rich diet for six months exhibited normal coronary artery vasodilation in response to locally-administered acetylcholine, whereas a vasoconstrictive response was seen in male animals as well as female monkeys with a low intake of phytoestrogens (54). In vitro studies of isolated vessels have examined the mechanisms of phytoestrogen–induced vasodilation (55). Estradiol-17B, genistein and daidzein were all found to relax mesenteric arterial rings of rats in a dose dependent manner. Consistent with receptor affinity assays, estradiol was the most potent vasodilator, followed by genistein, then daidzein. In these isolated arterial rings, response was independent of gender. The vasorelaxation was endothelium-independent and was not blocked by antagonists of nitric oxide or prostacyclin production.
Estrogen withdrawal results in symptomatic hot flashes in perimenopausal women and may represent an alteration in vasomotor response to endocrinologic stimuli. As a population, Asian women experience less perimenopausal hot flashes, a benefit attributed to phytoestrogens. Also, in a randomized study of 58 postmenopausal non-Asian women, those consuming soy protein supplementation in the form of 45 g of soy flour per day suffered less from hot flashes than control women (56), invoking another potential use for phytoestrogen supplementation.

Phytoestrogens may have electrophysiological effects as well. The sensitivity of ventricular myocytes to beta-adrenergic stimulation can be enhanced by genistein and daidzein, implicating a role of tyrosine kinase regulation of cardiac ion channels (57). However, there is, as yet, no known clinical effect of phytoestrogens on arrhythmias.

**BENEFICIAL NONCARDIOVASCULAR EFFECTS**

The most powerful argument against the routine use of HRT for postmenopausal women is the increased risk of cancer. Phytoestrogens do not appear to increase the risk of breast and uterine cancer; in fact, observations from in vitro and animal studies indicate that phytoestrogens may have antineoplastic effects. These antineoplastic effects may be related to suppression of angiogenesis, inhibition of tyrosine kinase activity, or partial antagonism of estrogen receptors. Tumor growth is dependent upon angiogenesis, which is a tightly regulated, complex process (58). Endothelial cells play a pivotal role in angiogenesis, which requires endothelial cell attachment, migration, proliferation, protease production and subsequent organization into vascular structures. Whereas estradiol has been demonstrated to augment various steps in the angiogenic process (59), components of phytoestrogens may actually inhibit angiogenesis. Genistein reduces basic fibroblast growth factor-induced endothelial cell migration (60) and capillary-like tube formation, perhaps by inhibiting tyrosine kinase or by decreasing levels of plasminogen activator and plasminogen-inhibitor and, thus, interrupting the tightly regulated balance of proteolytic degradation (25). In the setting of atherosclerosis, the enhancement of angiogenesis may hold therapeutic potential to relieve myocardial ischemia by increasing blood flow. Therapeutic angiogenesis has become a very active field of research with ongoing clinical studies designed to explore the safety and efficacy of various growth factors, delivered as protein or gene therapy. However, the neovascularization of atherosclerotic plaques could lead to plaque instability and resultant negative consequences. Indeed, Folkman and colleagues (61) have recently demonstrated that endostatin, an inhibitor of angiogenesis, can slow the development of aortic lesions in the hypercholesterolemic apoE-deficient mouse.

Phytoestrogens, particularly genistein, also have antiproliferative effects. This has been demonstrated in multiple cell lines including prostate cancer cells (62), breast cancer cells (both estrogen receptor positive as well as negative) (63) and other tumor cells (neuroblastoma, sarcoma, retinoblastoma), as well as vascular endothelial cells and fibroblasts (64). The in vitro effect of genistein, a known tyrosine kinase inhibitor, on breast cancer cell growth was evaluated by quantifying DNA and total cellular protein levels compared with the effect of estrogen (65). Over a range of 0.1 to 1 μM, genistein had a stimulatory, estrogen-like effect on estrogen receptor positive cell proliferation, but at >10 μM of genistein, growth was totally inhibited. However, estrogen receptor negative cells showed no response to, or possibly inhibition by, genistein even at low concentrations (10 nM–1 μM). Another group of investigators demonstrated that the effect of phytoestrogens in inhibiting proliferation is a reversible, cytostatic effect (60). Even at concentrations of up to 200 μmol/L, genistein was not cytotoxic in quiescent cells. The mechanism of this inhibitory effect of genistein is speculated to be its antagonism of tyrosine kinase. However, other investigators have observed a genistein-induced inhibition of proliferation despite adequate levels of tyrosine kinase activity (66). This antiepithelial effect of phytoestrogens may provide protection analogous to the estrogen partial-agonist, tamoxifen, in the treatment or prevention of breast cancer. Animal models support an antineoplastic role for phytoestrogens; for example, rats given soy-derived phytoestrogens develop fewer mammary tumors after exposure to carcinogens (67).

The evidence that phytoestrogens may protect against cancer development derives largely from in vitro studies of human cell lines, animal models of neoplasia and epidemiological data. Overall, most epidemiological studies have indicated a protective effect of soy ingestion (68). Epidemiologic studies reveal a decreased incidence of breast, prostate and endometrial cell cancer in populations ingesting high amounts of soy. Asian women develop breast cancer four to six times less often than their American counterparts, but this advantage wanes after living in the U.S. (69–71), implicating a protective influence of traditional diets. Furthermore, breast cancer patients have lower urinary isoflavone levels, suggesting that they have decreased ingestion, absorption, excretion or overall bioavailability of isoflavones compared with women without breast cancer (72,73). The benefits of dietary phytoestrogens may extend to other neoplasms, and to men as well as women. Hawaiians of Japanese descent who maintain a traditional diet with high soy content have less risk of prostate cancer than non-Japanese Hawaiians (74), and consumption of a diet enriched with lignans (legumes and fruit) is associated with decreased prostate cancer risk in Seventh Day Adventists (75). If these beneficial effects of diet are due to phytoestrogen content, the benefit may be linked to the observation that certain phytoestrogens (i.e., genistein and biochanin A) have been observed to inhibit the growth of androgen-dependent and independent human prostate cancer cell lines (62). High soy consumption (as tofu, miso or soybean sprouts) is associated with reduced risks of lung, gastric and
rectal cancer in Chinese and Japanese men and women (76–83). Rates of breast, ovarian, prostate and colon cancer are negatively correlated with cereal and phytoestrogen intake when comparing cancer mortality rates and food availability data among countries (84).

Despite the plethora of evidence that phytoestrogens have antineoplastic effects, two concerning clinical reports have been published. One study reported the effect upon monthly nipple aspirations in pre- and postmenopausal women ingesting soy protein containing 38 mg genistein/day (85). An increased total fluid volume was recovered in premenopausal women and postmenopausal women during and after phytoestrogen treatment. Additionally, there was an increased frequency of cellular hyperplasia in the aspirate. However, there were no controls in this study, and the aspirations themselves could account for the abnormalities. Nevertheless, the study does raise some concern for high risk patients. Another report of 29 women taking 60 g of soybean supplement daily found increased proliferation of breast lobular epithelium assessed by 3H-thymidine labeling (86). However, there are no human studies that have linked dietary phytoestrogens to the development of breast cancer.

Similar to other selective estrogen antagonists, phytoestrogens may also protect against osteoporosis. Studies of aging or ovariecotomized rats have shown that a soy protein diet protects against bone loss (87,88) although this effect is not mimicked by supplemental genistein (89), suggesting that some other component of soy protein may be responsible for the beneficial effect. However, a trial in postmenopausal women revealed an increase in bone mineral density in the lumbar spine after isoflavone supplementation (90).

**SUMMARY**

To conclude, there are accumulating data from epidemiologic studies, human trials, animal models and in vitro analysis to support the increased use of phytoestrogens, particularly in individuals at high risk of CVD. Favorable effects upon lipid profiles, vascular reactivity, angiogenesis and tumorigenesis have been attributed to the isoflavones genistein and, to a lesser extent, daidzein. The increasing availability data among countries (84).

REFERENCES


Gehm BD, McAndrews JM, Chien PY, Jameson L. Resveratrol, a polyphenolic compound found in grapes and wine, is an agonist for the estrogen receptor. PNAS 1997;94:14138–43.


factor stimulated proliferation of human breast cancer cells. Cell
67. Barnes S, Grubbs C, Setchell KDR, Carlson J. Soybeans Inhibit
Mammary Tumors in Models of Breast Cancer. In: Pariza M, editor,
Mutagens and Carcinogens in the Diet. New York: Wiley-Liss,
68. Messina MJ, Persky V, Setchell KDR, Barnes S. Soy intake and cancer
risk: a review of the in vitro and in vivo data. Nutr Cancer 1994;21:
69. Henderson BE, Bernstein L. The international variation in breast
cancer rates: an epidemiological assessment. Breast Cancer Res Treat-
70. Nebres MV, Mark HFL. Breast cancer among Asian women. Med
enterolactone and enterodiol and of equol in omnivorous and vegetar-
ian postmenopausal women and in women with breast cancer. Lancet
72. Severson RK, Nomura AMY, Grove JS, Stemmerman GN. A pro-
spective study of demographics and prostate cancer among men of
73. Mills PK, Beeson WL, Phillips RL. Cohort study of diet, lifestyle and
74. Haenszel W, Kurihara M, Segi M, Lee RKC. Stomach cancer among
75. Nagai M, Hashimoto T, Yanagawa H, et al. Relationship of diet to the
incidence of esophageal and stomach cancer in Japan. Nutr Cancer
76. Swanson CA, Mao BL, Li JY, et al. Dietary determinants of lung
cancer risk: results from a case-control study in Yunnan Province,
77. Hirayama T. Relationship of soybean paste soup intake to gastric
78. You WC, Blot WJ, Chang YS, et al. Diet and high risk of stomach
80. Hirayama T. Relationship of soybean paste soup intake to gastric
81. Koo LC. Dietary habits and lung cancer risk among Chinese females
83. Rose DP, Boyar AP, Wynder EL. International comparison of
mortality rates for cancer of the breast, ovary, prostate and colon and
84. Petreas NL, Barnes S, King EB, et al. Stimulatory influence of soy
protein isolate on breast secretion in pre- and postmenopausal women.
85. McMichael-Phillips DF. Proceedings of the Second International
Symposium on the Role of Soy in Preventing and Treating Chronic
Disease. St. Louis (MO): Protein Technology International, 1996:
35.
prevents bone loss in an ovariectomized rat model of osteoporosis. J
87. Dodge JA, Glasebrook AL, Magee DE, et al. Environmental estro-
gen: effects on cholesterol lowering and bone in the ovariectomized
Their effects on blood lipids and bone density in postmenopausal