Soy and Women's Health

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Introduction

In recent years, soy has received a great deal of attention for its potentially positive effects on human health, including maladies particular to women—perimenopausal hot flashes, postmenopausal bone loss, and breast cancer.

Studies in these areas are ongoing, and although data from the early trials sometimes conflict, there is a growing body of evidence that suggests that phytoestrogens—estrogen-like molecules abundant in plants—found in soy may benefit women's health.

Soy and Vasomotor Symptoms of Menopause

Vasomotor symptoms (hot flashes) are among the most bothersome symptoms reported by perimenopausal women. Hot flashes result from declining estrogen levels, and physicians often prescribe hormone replacement therapy (HRT) as a primary means to mitigate them. While HRT can be offered as a short-term treatment for relieving vasomotor symptoms, the evidence that the longer women take HRT, the greater the risk of developing severe health problems such as coronary artery disease and stroke limit the use of this therapy over the long term.[1]

Given the widespread publication of recent findings regarding the negative health effects of HRT, many women question their healthcare providers about potential alternatives to HRT, even for short-term use. To respond to these questions, health professionals need accurate information about the efficacy of alternatives, such as soy, to relieve these symptoms.

Soy is one of the best dietary sources of isoflavones, which are considered selective estrogen receptor modulators (SERMs). Two isoflavones found in soy are genistein and daidzein. Soy isoflavones have been hypothesized as being responsible for lower incidence of hot flashes as early as 1992.[2] While the frequency and severity of vasomotor symptoms vary from woman to woman, Asian women generally report fewer symptoms than U.S. and European women.[3, 4] Interestingly, American women of Japanese or Chinese descent in one study were approximately one-third as likely to report having hot flashes compared to Caucasian women.[5] The first trial examining the efficacy of soy for the alleviation of menopausal symptoms was conducted in 1995.[6]

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In this study, Murkies et al. reported that hot flashes significantly and rapidly decreased in the intervention group of women given soy flour compared to those who received wheat flour.

Since then, 19 trials in 19 nations have explored the effects of soy foods or isoflavones on the frequency and/or severity of hot flashes. A recent meta-analysis[7] conducted by Messina and Hughes examined these studies. Thirteen of the 19 trials were parallel studies and involved more than 1,700 women. The studies ranged in length from 1 to 24 months, and isoflavone dose ranged from 34 mg to 100 mg isoflavones per day, primarily ≥70 mg/day or more. By comparison, Japanese adults typically consume 35–40 mg of isoflavones per day. Data from six studies were excluded from the analysis for the following reasons: two involved breast cancer patients, two reported on hot flash severity but not frequency, one was not blinded, and one failed to have a control group. Regression analysis of the data from the remaining 13 trials revealed a statistically significant relationship (P=0.01) between the frequency of hot flashes and treatment efficacy. Frequency of hot flashes decreased by five percent (taking into account placebo or control effects) for every additional hot flash per day in subjects who initially reported five or more hot flashes per day (study baseline).

Krebs et al.[8] conducted a review to evaluate the efficacy and tolerability of phytoestrogens for menopausal symptoms. They reviewed 25 trials involving 2,348 symptomatic perimenopausal or postmenopausal women who participated in randomized trials of soyfoods, soy extracts, and red clover extracts. A trial was included in the review only if it compared phytoestrogen with placebo or control, reported hot flash frequency or menopausal symptom scores, and was at least four weeks in duration. The authors found that seven of the eight soyfood trials reporting hot flash frequency outcomes did not show improvement in the group consuming more phytoestrogens compared to the control group. Of the five soyfood trials that demonstrated small- to medium-effects, three trials showed effects in the placebo group while two demonstrated effects in the soy group. Three of the five soy extract trials that examined hot flash frequency were negative. The degree of effect was calculated in two soy extract trials—the results of one trial favored placebo and while the other favored soy. The authors conclude that available evidence suggests that phytoestrogens available as soyfoods, soy extracts, and red clover extracts do not improve menopausal symptoms or hot flashes.

While both menopausal women and health professionals seek alternatives for treating hot flashes of menopause, the data on soy intake to alleviate these symptoms remains mixed.

Soy and Osteoporosis

It has been reported that perimenopausal women lose approximately 1–3 percent of their bone during the first years of menopause,[9, 10, 11] followed by an ongoing loss of 0.7–1 percent per year thereafter[12, 13, 14] due to the depletion of endogenous estrogen. Estrogen replacement therapy (ERT) is known to be an effective strategy to stabilize bone mineral density and preventing vertebral fractures. Due to the recent reports of increased health risks and the uncomfortable side effects ERT causes, postmenopausal women have been found to be less than 20 percent compliant when taking this therapy.[15]

While research to date is inconclusive, some study data suggest that soy phytoestrogens may benefit bone health.

With their weak estrogenic activity, isoflavones have been found to have an affinity for estrogen receptor-ß (ER-ß). Knight et al.[16] reviewed several studies that demonstrated a lower incidence of hip osteoporosis among Asian populations that consumed more soy in their diets when compared to Western populations. Studies on rats that have had their ovaries removed have shown similar bone-sparing effects of 17ßestradiol and soy protein isolate[17], genistein or daidzein,[18] or their succinylated (chemically modified) products following soybean fermentation.[19]

Ho et al.[20] examined the effect of habitual soy intake and soy-derived isoflavones supplementation on bone mass in early postmenopausal Chinese women. The cross-sectional study investigated if there was an association between habitual dietary soy protein/isoflavones intake and bone mass in a population-based sample of 454 healthy Chinese women (mean age 55.1 years) within the first 12 years following menopause. Among the older postmenopausal women, the authors found a dose-relationship between soy intake and bone mineral density values at the trochanter, intertrochanter and total hip and total body. It appeared that the greater the soy intake, the greater the bone mineral density.

Chen et al.[21] conducted a trial to examine the effects of soy-derived isoflavones on bone loss in 203 postmenopausal Chinese women, aged 48 to 62 years. The subjects were randomly assigned to one of three groups to receive on a daily basis either placebo (0 mg), mid-dose (40 mg), or high-dose (80 mg) isoflavone supplementation. All subjects received 500 mg calcium and 125 IU vitamin D3. The study investigators reported a more marked effect of soy supplementation on hip bone mineral content (total hip and trochanter) in older menopausal women or in those women with lower calcium intake and lower body weight.

Recently Lydeking-Olsen et al.[22] reported results from a two-year randomized, double-blind study that compared the intervention effects of soymilk with isoflavones, transdermal progesterone, the two interventions combined, or a control treatment (isoflavone-poor soymilk and progesterone-free cream) on bone measures. Postmenopausal women with three risk factors for osteoporosis or blatant osteoporosis participated in the study. Dual-energy x-ray absorptiometry (DEXA) was used to assess bone mineral content and bone mineral density of the lumbar spine and hip. The percent change in the bone mineral content and bone mineral density did not differ from zero (no gain nor loss noted) in both the daily intake of two glasses of soymilk containing 76 mg isoflavones and the transdermal progesterone. However, significant bone loss was noted in the control group and in the combination treatment group. Elucidation of the interaction between soymilk and transdermal progesterone warrants additional investigation.

Messina and colleagues[23] reviewed 15 studies examining skeletal effects of soybean isoflavones. Most of the studies were small (fewer than 30 participants per group) and

lasted one year or less. Though the findings were somewhat inconsistent, the data generally suggested that isoflavones can reduce bone loss in younger menopausal women. The limited epidemiological data demonstrated that isoflavone intake among Asian populations was generally associated with higher bone mineral density. The authors concluded that though soyfoods and isoflavones should not be considered substitutes for anti-osteoporotic medications, health professionals could consider encouraging postmenopausal women who are concerned about osteoporosis to incorporate soy into their diets.

Gallagher and colleagues[24] arrived at a different conclusion as a result of their trial. Sixty-five women, with 7.5 years since menopause and whose mean age was 55 years, were randomized into three groups. One group received daily soy protein with 96 mg of isoflavones, another received soy with 52 mg of isoflavones daily, while the final group received soy without isoflavones (<4 mg isoflavones per day). Each group was given soy for nine months. Participants were then followed for six months after they stopped consuming soy. The level of serum isoflavones at three months showed dose-related increases in all three groups. But there was no significant effect of the supplements on bone mineral density of the spine or femoral neck. Bone mineral density increased in the trochanter at 9 and 15 months in the group given isoflavone-free soy compared to the other two groups. In this trial, the authors did not find a significant positive effect of soy protein isolate supplemented with isoflavones on bone mineral density.

Understanding the role that soy plays in bone health is in its earliest stages, and the initial findings, while somewhat mixed, appear promising. More research to characterize the manner in which soy acts on bone tissue as well as long-term randomized controlled trials are needed to ascertain the role of soy protein and soy isoflavones on bone mineral content and density and fracture incidence.

Soy and Breast Cancer

Breast cancer mortality rates among populations that regularly consume soyfoods, along with data showing that weak estrogens may act as antiestrogens, prompted initial speculation that soy intake may reduce breast cancer risk.

In a study conducted using an animal model, isolated soy protein was shown to counter the effects of estrogen on mammary cell proliferation in monkeys.[25] During the past decade, researchers have identified several different mechanisms by which soy may wield an antiestrogenic effect. These mechanisms include antioxidant effects, or its ability to lower plasma and urinary concentrations of estradiol and its metabolites by increasing gut excretion[26] estrogen/antagonism, topoisomerase inhibition, aromatase inhibition, angiogenesis inhibition, and promotion of apoptosis.[27]

Interest regarding the anticancer effects of soy comes from research examining genistein and its ability to inhibit the activity of key enzymes and to influence molecules that lead to the inhibition of cancer cell growth. Constantinou[28] reported that genistein seems to trigger the pathway that leads to cellular differentiation by stabilizing protein-linked DNA strand breakage. Fotsis and colleagues[29] found evidence that genistein inhibited

cell proliferation and in vitro angiogenesis, while the animal model research of Iishi et al.[30] demonstrated that the isoflavone attenuated cancer metastasis by inhibiting invasion of cancer cells into the lymphatic vessels.

However, there is concern is that the estrogen-like effects of isoflavones may stimulate the growth of existing breast tumors or increase risk in women at high risk of developing breast cancer.[31] Large randomized clinical trials involving postmenopausal women[32, 33] and other published research[34] suggest that when combined, estrogen and progestin markedly increases breast cancer risk while estrogen alone does so either weakly or not at all. Therefore, the estrogen-like qualities of soy isoflavones are unlikely to have the same effect as estrogen and progestin therapy.[35]

Research by Helferich and colleagues demonstrated that both isolated soy protein and genistein stimulated the growth of mammary tumors in mice that had their ovaries removed implanted with estrogen-sensitive breast cancer cells[36] and in rats injected with a mammary carcinogen.[37] However, isoflavones have been shown to inhibit the growth of tumors in mice with intact ovaries that have been implanted with estrogen-sensitive breast cancer cells.[38] It can be argued that mice with ovaries better reflect the situation in women with breast cancer because in this animal model—as with pre- and postmenopausal women—breast tumors can grow without an externally supplied source of estrogen. In mice without ovaries, tumors do not grow unless external estrogen is supplied.[35] Thus in this animal model, isoflavones stimulate tumor growth only when estrogen levels appear to be much lower than those that exist in postmenopausal women.

Human studies published in 1996[39] and 1998[40] suggested that soy exerted effects similar to estrogen on breast tissue. However, the 1996 study did not have a control group. The finding from the 1998 study—that there was an increase in breast cell proliferation in premenopausal women after two weeks of soy consumption—were not confirmed when the complete analysis was published.[41] Another two-year trial showed the consumption of soy foods providing 50 mg isoflavones each daily did not affect breast tissue density in premenopausal women.[42] Increased breast tissue density is considered to be breast cancer risk factor.[43, 35]

A small clinical trial of short duration yielded interesting results. Sartippour[44] and colleagues examined the effects of 200 mg of isoflavone supplements (nearly four times the amount typically consumed by a Japanese adult) for a two-week period following breast cancer diagnosis (core-needle biopsy established the breast cancer diagnosis). Control cases (historical) similar to the experimental patients were selected for comparison. Blood samples and breast tissue obtained from core biopsies were analyzed before and after the administration of isoflavones. There were no statistically significant effects of isoflavones. But in the isoflavone treatment group, there was a statistically nonsignificant trend toward cancer growth inhibition. Though the trial was of short duration and involved a small number of subjects, it suggested that isoflavones may not adversely impact breast tumors at this dose over this period of time.

Overall, there is little evidence that soy or isoflavones increase breast cancer risk in healthy women or increase the risk of developing secondary tumors in breast cancer patients. However, the issue of whether the latter group should consume soy remains controversial.

Conclusion

Scientific inquiries investigating the effects of soy and its isoflavones on vasomotor symptoms, bone health, and breast cancer are yielding some intriguing results. Soy and its isoflavones have had mixed results in demonstrating reduction in severity and frequency of hot flashes. Soy also appears promising in its ability to slow the bone loss of postmenopausal osteoporosis. It is evident that much more research is required to understand isoflavone effects in breast tissue.

There is enough evidence to suggest that a moderate amount of soyfood intake is likely to be beneficial rather than harmful to overall health. However, until further investigations regarding the effect of isoflavones in breast tissue, in particular, survivors of estrogen-receptor positive breast cancer may consider avoiding high levels of isoflavone consumption.

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