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Do Soy Isoflavones Cause Endometrial Hyperplasia?

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For many years, hormone replacement therapy (HRT) was considered the gold standard for the symptomatic treatment of menopause. Clinical trials have found that HRT reduces the symptoms of hot flashes and sweating, while also decreasing vaginal dryness and urinary tract infections. HRT has also been shown to be protective against colon cancer (37%) and hip fractures (34%). However, recent findings from the Women's Health Initiative (WHI) have revealed that long-term HRT may actually lead to an increase in heart disease (29%), breast cancer (26%) and other adverse events, such as stroke (41%). Consequently, many women in the United States and abroad are actively looking for alternative treatments for menopause, including botanical dietary supplements.

Key words: endometrial hyperplasia, isoflavones, menopause, soy

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INTRODUCTION

A recent survey of peri- and menopausal women at the University of Illinois at Chicago found that 79% of US women were using botanical dietary supplements, 65% for the treatment of menopausal symptoms such as hot flashes, joint pain, and insomnia, as well as depression, anxiety, and fatigue.[1] Commonly used supplements for the treatment of menopausal symptoms include *Angelica sinensis* (dong quai), *Panax ginseng* (ginseng), *Oenethera biennis* (evening primrose oil), *Actaea racemosa* L. syn *Cimicifuga racemosa* L. (black cohosh), *Trifolium pratense* L. Nutt (red clover), and *Glycine max* Merril (soy). Approximately 42% of the women in this survey were using soy products, including soy milk, soy protein, and soy isoflavones.[1]

The hypothesis that soy may reduce menopausal symptoms originated from epidemiological data suggesting that hot flashes occur much less frequently in Asian women than in Western women.[3,4] For example, a 2001 cohort study of Japanese women revealed an inverse relationship between soy intake and hot flashes.[4] However, reviews of the clinical trials assessing the effects of soy are difficult to perform due to variations in products used (from soy foods to purified isoflavones), dosage, scoring systems for symptoms of hot flashes, and the menopausal status of patients.[5] Studies have also been of short duration; only three of the eight studies with treatment phases lasting more than 6 weeks showed significant improvement in hot flashes at the end of the study, and most benefits disappeared after 6 weeks.[6] The longest study to date showed no benefit for hot flashes (or other symptoms) at 24 weeks.[7] In a few studies, menopausal symptoms decreased in all groups—often by as much as 50% to 60%—in placebo as well as treatment groups. In contrast, two trials have reported a significant reduction in hot flashes in a soy-treated group compared with a placebo-treated group.[6,8] Hot flash frequency was reduced by 45% and 28%, respectively, compared with placebo, although the dose used and the modes of administration were not well defined.[5]

Reports of adverse events associated with soy intake have been few. However, Unfer et al.[9] recently reported the results of a 5-year randomized double-blind, placebo-controlled clinical trial that assessed the endometrial effects of soy isoflavones in postmenopausal women. That study involved 376 postmenopausal healthy women ages 45 to 60 who had no menstruation for at least 6 months prior to the initiation of the investigation, and all of whom had an intact uterus. The women were distributed into two different groups using randomized criteria: group A (n = 179) patients received soy isoflavones in a dose of 150 mg of isoflavones per day for 5 years (the product was described as 600 mg tablets containing 50 mg of soy isoflavones consisting of 40% to 45% genistein, 40% to 45% daidzein, and 10% to 20% gly-

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citein); group B (n = 197) patients received identical appearing placebo tablets for 5 years.

The primary outcome measured was the results of endometrial histology from biopsies obtained at baseline, 30 months, and 5 years after the beginning of the treatment (298 women completed the 5-year treatment). No cases of malignancy were detected during biopsy. Seventy percent of women undergoing treatment with soy phytoestrogens had an endometrium classified as atrophic or non-assessable, compared with 81% receiving placebo. The occurrence of endometrial hyperplasia was significantly higher in the soy group at the 5-year mark (3.37% vs. 0%; total of 4 cases of hyperplasia at 5 years). No cases of hyperplasia were observed at 30 months. The endometrial hyperplasia was first detected after 5 years, and most of the cases had simple hyperplasia, which indicates a weak estrogenic effect of isoflavones on the endometrium.

EPIDEMIOLOGICAL STUDIES

The soy isoflavones are comprised primarily of the glucosides genistin and daidzin and their respective aglycones, genistein (4′5, 7-trihydroxyisoflavone) and daidzein (4′,7-dihydroxyisoflavone).[10] These compounds are considered to be phytoestrogens (plant-derived estrogens) because they bind to estrogen receptors and exert weak, estrogen-like effects in vitro and in vivo.[10,11] It has been suggested that isoflavones may be selective estrogen receptor modulators, due to preferential binding to and activation of estrogen receptor-β compared with estrogen receptor-α.[12] Therefore, isoflavones may act as weak estrogens on the uterus.

It is well known that unopposed moderate- or high-dose estrogen therapy in women with an intact uterus is associated with a significant increase in rates of endometrial hyperplasia and cancer.[13] Despite the differences between isoflavones and estrogens, there is still concern that isoflavones may exert estrogenic effects on hormone-sensitive tissues and, as a result, potentially increase the risk of endometrial hyperplasia and cancer. However, epidemiological studies suggest that isoflavones may actually reduce the risk of cancer rather than increase it. For example, one large case control study of a multi-ethnic population in Hawaii found that a high consumption of tofu and other soy products was associated with a decreased risk of endometrial cancer.[13] In this study, high consumption of soy products and other legumes was associated with a decreased risk of endometrial cancer (P for trend = 0.01; odds ratio = 0.46, 95% confidence interval 0.26–0.83) for the highest compared with the lowest quartile of soy intake.

These dietary associations may explain in part the reduced rates of uterine cancer in Asian countries compared with those in the United States. In fact, Asian women have approximately 1/10 the risk of endometrial cancer as Caucasian women living in Western nations.[13,14] A recent population-based case-control study with detailed information on usual soy food intake was performed using a food frequency questionnaire. In that study, 832 incident cases of endometrial cancer in women aged of 30 to 69 years diagnosed between 1997 and 2001 were identified from the Shanghai Cancer Registry; 846 control women were matched to cases on age and randomly selected from the Shanghai Residential Registry. The study concluded that regular consumption of soy-containing foods, measured as amount of either soy protein or soy isoflavones, was inversely associated with the risk of endometrial cancer.[15]

ANTI-ESTROGENIC EFFECTS OF SOY IN PREMENOPAUSAL WOMEN

Evidence for the anti-estrogenic effects of soy was shown by Nagata et al.,[4] who found that in a study of 50 young regularly cycling Asian women, the intake of soy products was inversely correlated with serum E1 and E2 levels. Premenopausal Japanese women were randomly assigned to receive either a soy milk-supplemented diet (n = 31) or a normal (control) diet (n = 29). The women in the soy milk-supplemented group were asked to consume about 400 mL of soy milk (containing about 109 mg of isoflavones) daily during a study period that involved three consecutive menstrual cycles. Follicular-phase blood samples were to be obtained in the menstrual cycles preceding (cycle 1) and following (cycle 3) the 2-month dietary intervention. At the end of the study period, estrone and estradiol levels were decreased by 23% and 27%, respectively, in the soy milk-supplemented group and were increased by 0.6% and 4%, respectively, in the control group.[4] These data suggest that regular consumption of soy milk may actually protect against estrogen-induced cancers by reducing the serum estrogen levels over the lifetime of premenopausal women.

ANTI-ESTROGENIC EFFECTS OF SOY ISOFLAVONES IN ANIMAL MODELS

The effects of genistein and daidzein on endometrial carcinogenesis in mice have also been investigated.[16] Single subcutaneous administration of genistein (1 mg/30 g body weight) for 2 weeks significantly decreased the levels of 17-β-estradiol (5 ppm in diet)-induced expression of c-jun, interleukin-1α (IL-1α), and tumor necrosis factor-α (TNF-α) mRNAs in the uteri of ovariectomized mice ($P < 0.005$, $P < 0.05$, and $P < 0.01$, respectively). Daidzein significantly inhibited estradiol-induced expression of c-fos and IL-1α ($P < 0.01$ and

$P < 0.01$, respectively). In the 30-week study, mice were given N-methyl-N-nitrosourea-containing solution and normal saline (as controls) into their left and right uterine corpora, respectively, and divided into six groups. Group 1 was given estradiol (in the diet) alone; group 2 was given estradiol and genistein (1 mg/30 g body weight subcutaneously every 4 weeks); group 3 was exposed to estradiol and daidzein (1 mg/30 g body weight subcutaneously every 4 weeks); groups 4 and 5 received genistein and daidzein, respectively, and were kept on the basal diet; group 6 was kept on the basal diet and served as a control. At the end of the experiment, incidences of endometrial adenocarcinoma and atypical endometrial hyperplasia of the group given estradiol and genistein or daidzein were significantly lower than those of the group with estradiol alone ($P < 0.01$ and $P < 0.05$, respectively). It is suggested that both genistein and daidzein have an inhibitory effect on estrogen-related endometrial carcinogenesis in mice, possibly by suppressing expression of the estrogen-induced, estrogen-related genes c-fos and c-jun and internal cytokines IL-1α and TNF-α through a cytokine and estrogen receptor-mediated pathway.[16]

In a more recent study, this same group examined the inhibitory effects of soybean isoflavones on estrogen-stimulated gene expression in the uteri of ovarectomized mice.[17] Subcutaneous administration of genistin (glycoside of genistein) significantly decreased the levels of 17-β-estradiol-17-β-induced expressions of c-jun, IL-1α and TNF-α mRNAs ($P < 0.005$, $P < 0.05$, and $P < 0.05$, respectively) and proteins in the mice uteri. Daidzin (glycoside of daidzein) weakly inhibited E2-stimulated expressions of c-fos and IL-1α. Both genistin and daidzin had a weaker inhibitory effect than that of genistein and daidzein on the expression of estrogen-stimulated genes.[17]

LACK OF ENDOMETRIAL PROLIFERATION AFTER ISOFLAVONE ADMINISTRATION

Several human studies have investigated the effect of varying doses of isoflavones on endometrial proliferation, and have shown that oral administration of a diet high in isoflavones or isoflavone supplements to postmenopausal women does not increase endometrial thickness when measured by transvaginal ultrasound.[18-21] Hale et al.[22] studied the effect of a 3-month course of a 33 mg red clover isoflavone supplement on the Ki-67 proliferative index in endometrial tissue specimens taken between days 8 and 11 of the menstrual cycle. In this study of 30 late reproductive-aged and perimenopausal women, there was no difference in the endometrial Ki-67 index or endometrial thickness between the soy isoflavone and placebo groups.[22] The estrogenic effects of three soy extracts, each containing different concentrations of isoflavones, were then assessed in postmenopausal women.[18]

Isoflavones were consumed relative to bodyweight (control: 0.11 ± 0.01; low isoflavone: 1.00 ± 0.01; high isoflavone: 2.00 ± 0.02 mg/kg/d) for 93 days each in a randomized crossover design. The high-soy diet resulted in a small but significant decrease in estrone-sulfate, a trend toward lower estradiol and estrone, and a small but significant increase in SHBG (sex hormone-binding globulin). There were no significant effects of the low-soy or high-soy diets on vaginal cytology or endometrial biopsy results. The results of this study showed that none of the extracts produced an estrogenic effect on vaginal epithelium or endometrium of treated women.[18]

Nikander et al.[23] performed a double-blind, randomized, placebo-controlled crossover trial to assess the effects of soy-derived isoflavones on vaginal epithelium and the endometrium. Sixty-four postmenopausal women with a history of breast cancer ingested 114 mg of isoflavones or placebo daily for 3 months. The treatment regimens were crossed over after a 2-month washout period. The main outcomes measured included vaginal dryness, maturation index of vaginal epithelium, endometrial thickness, histology, and expression of estrogen and progesterone receptors and the proliferation marker Ki-67 in the endometrium. The results showed that isoflavones did not relieve vaginal dryness, maturation index values remained the same, and no changes were found in any of the variables measured in the endometrium. Thus, in this study, daily administration of 114 mg of isolated isoflavones for 3 months had no effect on the subjective perception of vaginal dryness or on objective findings in the vagina or endometrium.[23]

Balk et al.[24] performed another study to assess endometrial histology in postmenopausal women and to evaluate adverse events and efficacy of isoflavones in treating menopause-associated symptoms. This was a prospective, double-blinded, randomized, placebo-controlled trial comparing the effects of 6 months of dietary isoflavone supplementation versus placebo in postmenopausal women. Baseline endometrial biopsies were performed and, if adequate, non-hyperplastic, non-cancerous, and non-ovulatory subjects were randomly assigned to receive daily placebo or soy cereal supplementation for 6 months. Study subjects completed baseline and weekly dietary, symptom, and side effect logs. Repeat endometrial biopsies were obtained at 6 months. Twenty-seven subjects were randomized, and 19 completed the study. One (3.7%) baseline endometrial sample was weakly proliferative. All other baseline and final biopsies were consistent with atrophic, inactive endometrium.[24]

A prospective, open, randomized clinical trial was performed to evaluate the effects of isoflavones on cli-

macteric-related symptoms and on the endometrium in postmenopausal women.[25] Seventy postmenopausal women were randomly assigned to two treatment groups receiving 12 cycles of treatment with either genistein (group A) or calcium (group B). In all patients, ultrasonographic endometrial thickness and Kupperman index were evaluated at baseline and after 6 and 12 cycles of treatment. At baseline, no significant difference was detected in endometrial thickness or Kupperman index between groups A and B. After 6 and 12 cycles of treatment, no significant difference was observed in endometrial thickness between or within groups. Endometrial thickness was less than 5 mm in all cases before and during treatment (except in two cases in group B and in one case in group A) after 12 months. At 6 and 12 months, the Kupperman index was significantly ($P < 0.05$) lower in group A compared with baseline values and group B. The study concluded that genistein administration may reduce climacteric symptoms in postmenopausal women and does not increase endometrial thickness.[25]

In one study published in 2004, the effects of the phytoestrogen genistein, estrogen-progestogen therapy, and placebo on hot flashes and endometrial thickness were assessed in postmenopausal women.[26] Ninety healthy, postmenopausal women 47 to 57 years of age were randomly assigned to receive continuous estrogen-progestogen therapy for 1 year (n = 30; 1 mg 17-beta-estradiol combined with 0.5 mg norethisterone acetate), genistein (n = 30; 54 mg/d), or placebo (n = 30). Endometrial safety was evaluated by intravaginal ultrasounds at baseline and at 6 and 12 months. The results showed that, compared with placebo, daily hot flashes were reduced significantly by a mean of 22% (95% confidence interval: −38 to −6.2; $P < 0.01$) after 3 months, by a mean of 29% (95% confidence interval: −45 to −13; $P < 0.001$) after 6 months, and by a mean of 24% (95% confidence interval: −43 to −5; $P < 0.01$) after 12 months of genistein treatment. No side effects were observed on the uteri of the participants.[26]

ESTROGENIC EFFECTS OF SOY

Soy isoflavones interact with the mammalian estrogen receptor and appear to have both estrogen-agonist and estrogen-antagonist effects on mammalian physiology, depending on the tissue involved and the concentration or doses used in the study.

Studies in rodents have shown that isoflavones act as weak estrogens by stimulating an increase in plasma prolactin levels, mammary gland proliferation, and uterine weight, as well as altering vaginal cytology in ovariectomized rats.[27] Furthermore, two of the soy isoflavones, daidzin and genistin, have been shown to prevent bone loss when administered orally to ovariectomized rats.[28,29] Genistein also acts as an estrogen agonist, resulting in the proliferation of cultured human MCF-7 breast cancer cells.[30]

Kayisli et al.[31] investigated the effects of the five major soy isoflavones (daidzein, daidzin, genistein, genistin, and glycitin) in an endometrial stromal and glandular cell proliferation assay, cellular ELISA for proliferating cell antigen, and an alkaline phosphatase assay.[31] The isoflavones genistein, daidzin, and glycitin induced endometrial stromal cell proliferation that occurred only at high concentrations, but this effect was still 8% to 15% lower than cell proliferation induced by estradiol. In the presence of estradiol, however, the isoflavones antagonized the proliferative effect of estradiol by 10% to 20%, which indicates that isoflavones have anti-estrogenic effects when combined with physiological concentrations of estradiol.[31]

Foth and Cline[32] investigated the effects of combining estrogen with soy in four groups of ovariectomized adult macaque monkeys fed either no hormone treatment (0), oral E2 (E), oral soy protein isolate (soy), or both E2 and the soy protein (E + soy). After 6 months of treatment, histopathological assessment of both mammary and endometrial sections showed a significant decrease in the Ki-67 proliferative index in the E + soy group compared with the E group.[32] However, there was no significant difference between endometrial thickness in the E and the E + soy group, indicating no additive effect on the endometrium.

Tansey et al.[33] investigated the possible anti-uterotropic properties of isoflavone administration in rats, and found that the administration of isoflavone-rich soy protein plus steroidal estrogen caused a significant reduction in uterine luminal epithelial height and uterine lactoferrin expression compared with steroidal estrogen alone. There was, however, no change in uterine weight or uterine proliferation as measured by immunohistochemical staining for proliferating cell nuclear antigen. When isoflavone-rich soy protein was administered without estrogen, the high dose (118 mg isoflavones per 1800 calories), but not the low dose (11.8 mg isoflavones per 1800 calories), caused a non-significant increase in uterine weight.[33] In another study using the murine model, dietary genistein was administered at doses of 125, 375, and 750 μg/g feed. The two higher doses caused significant increases in uterine weight when administered together with 17-β-estradiol,[34] and none of the three doses of genistein was shown to reverse the E2-induced increase in uterine weight. No other markers of uterine or endometrial proliferation were measured. In another rat model study, genistein was shown to cause a dose-dependent inhibition of progesterone production from

cultured ovarian cells and, at high doses, an inhibition of progesterone production from granulosa cells.[35] The inhibitory effect of genistein on steroidogenesis in this study appeared to be independent of cytokines and growth factors.[35]

CONCLUSIONS

At least eight clinical trials and numerous other pharmacological investigations have assessed the effects of soy on menopausal symptoms. None of these investigations has reported any incidence of endometrial hyperplasia as an adverse event after treatment with soy isoflavones and/or protein. In the Unfer study,[9] only 3.37% of the women treated with soy isoflavones developed hyperplasia (a total of four women), which was not observed until after 5 years of therapy. The two primary differences in this investigation were the very high dose of isoflavones (150 mg/d) and the long treatment period of 5 years, which was significantly longer than any other previously published study. Considering that the average recommended dose of isoflavones in the United States is 40 to 80 mg/d, the dose used in the Unfer study is two to three times higher. This dose was much higher than those used in other clinical studies, and there are no clinical trials supporting the use of this dose for any therapeutic indication. Thus, the dose used in the Unfer study was atypical, and it would have been much more informative to have included a lower-dose arm of the study (80 mg/d) for comparison purposes. In addition, some of the patients had high BMIs, and there is little information given to indicate whether the hyperplasia was observed in the obese patients, since obesity alone is a risk factor for endometrial hyperplasia. At 30 months there were no cases of hyperplasia in any of the subjects, and at 5 years, nearly 75% had an atrophic or inactive endometrium showing no direct estrogenic effect.

Review of the clinical and pharmacological data suggests that soy isoflavones do not cause endometrial hyperplasia when used in normal therapeutic doses. In fact, for premenopausal women, the data actually suggest that soy ingestion may protect against endometrial hyperplasia and cancer, because in the presence of estrogen, soy isoflavones appear to act as anti-estrogens. Furthermore, based on the data reviewed here, there does not appear to be any rationale for recommending a 150 mg/d dose of soy isoflavones for postmenopausal women.

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