Soy Isoflavones in the Prevention of Menopausal Bone Loss and Menopausal Symptoms

A Randomized, Double-blind Trial

Silvina Levis, MD; Nancy Strickman-Stein, PhD; Parvin Ganjei-Azar, MD; Ping Xu, MPH; Daniel R. Doerge, PhD; Jeffrey Krischer, PhD

Background: Concerns regarding the risk of estrogen replacement have resulted in a significant increase in the use of soy products by menopausal women who, despite the lack of evidence of the efficacy of such products, seek alternatives to menopausal hormone therapy. Our goal was to determine the efficacy of soy isoflavone tablets in preventing bone loss and menopausal symptoms.

Methods: The study design was a single-center, randomized, placebo-controlled, double-blind clinical trial conducted from July 1, 2004, through March 31, 2009. Women aged 45 to 60 years within 5 years of menopause and with a bone mineral density T score of –2.0 or higher in the lumbar spine or total hip were randomly assigned, in equal proportions, to receive daily soy isoflavone tablets, 200 mg, or placebo. The primary outcome was changes in bone mineral density in the lumbar spine, total hip, and femoral neck at the 2-year follow-up. Secondary outcomes included changes in menopausal symptoms, vaginal cytologic characteristics, *N*-telopeptide of type I bone collagen, lipids, and thyroid function.

Results: After 2 years, no significant differences were found between the participants receiving soy tablets (n=122) and those receiving placebo (n=126) regarding changes in bone mineral density in the spine (–2.0% and –2.3%, respectively), the total hip (–1.2% and –1.4%, respectively), or the femoral neck (–2.2% and –2.1%, respectively). A significantly larger proportion of participants in the soy group experienced hot flashes and constipation compared with the control group. No significant differences were found between groups in other outcomes.

Conclusions: In this population, the daily administration of tablets containing 200 mg of soy isoflavones for 2 years did not prevent bone loss or menopausal symptoms.

Trial Registration: clinicaltrials.gov Identifier: NCT00076050

Arch Intern Med. 2011;171(15):1363-1369

Author Affiliations: Geriatric Research, Education, and Clinical Center, Miami Veterans Affairs Healthcare System, and Departments of Medicine (Dr Levis), Epidemiology (Dr Strickman-Stein), and Pathology (Dr Ganjei-Azar), Miller School of Medicine, University of Miami, Florida; Department of Pediatrics, University of South Florida, Tampa (Ms Xu and Dr Krischer); and National Center for Toxicological Research, US Food and Drug Administration, Jefferson, Arkansas (Dr Doerge).

THE INITIAL YEARS OF MENOpause often are associated with rapid bone loss, hot flashes, vaginal dryness, and sleep disturbances, among other symptoms. Estrogen therapy with or without progesterone prevents most of these changes. However, as a result of the Women's Health Initiative findings suggesting that the overall risks outweigh the benefits, most menopausal women now decline estrogen therapy,[1-3] increasingly seeking other alternatives. Soy-derived products have been proposed to provide comparable benefits to estrogens but without the risks.[4]

The lower prevalence of osteoporotic fractures, breast cancer, and cardiovascular disease in women in Asia has been attributed to their typically soy-rich diet.[5] Most epidemiologic and prospective studies[6,7] in Asian women consuming typical Asian diets suggest a beneficial skeletal effect of soy foods. On the basis of this information, Western women have significantly increased their consumption of soy products in the past decade.[8] Soy protein contains phytoestrogens (ie, the isoflavones genistein and daidzein), which bind to the estrogen receptor and can elicit a weak agonist, antagonist, or partial agonist-antagonist response, depending on the compound and the target tissue. Given the difficulty in changing dietary habits, most prospective studies of soy isoflavones in Western women have used tablets or foods fortified with isoflavones extracted from soy protein. Most trials have been limited by their short duration, low dose of isoflavones, assessment of a single outcome, small number of participants, and enrollment of women with a wide age range and varied menopausal status.[9] The

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objective of the Soy Phytoestrogens As Replacement Estrogen (SPARE) study was to test multiple outcomes in women in the first 5 years of menopause receiving a soy isoflavone dose equivalent to approximately 2 times the highest intake through food sources in typical Asian diets, thus ensuring an effective dose. We hypothesized that a 2-year intervention with a daily intake of 200 mg of soy isoflavones would preserve bone mineral density (BMD), maintain vaginal estrogenization, and prevent hot flashes.

METHODS

DESIGN OVERVIEW

The SPARE study, a single-site, parallel group, double-blind, randomized, placebo-controlled clinical trial was conducted from July 1, 2004, through March 31, 2009.[10] The study protocol was approved by the University of Miami's Human Subject Research Office. All participants provided written informed consent.

STUDY PARTICIPANTS

The study targeted women ages 45 to 60 years who had been menopausal for 1 to 5 years or for 6 to 12 months and had a follicle-stimulating hormone level of 40 mIU/mL or greater (to convert to international units per liter, multiply by 1). Participants were recruited from the South Florida area by direct mailings, posters, and presentations to community organizations. Potential participants were prescreened in a telephone interview; those who passed the interview were scheduled for a clinic screening visit. Women were not eligible to participate if they had osteoporotic fractures, a BMD T score in the lumbar spine or total hip of less than −2.0, body mass index (calculated as weight in kilograms divided by height in meters squared) of 32 or higher, abnormal mammogram findings, or cancer in the past 10 years (except for skin cancer) or were taking bone active drugs, corticosteroids, or herbal products. Those receiving menopausal hormone therapy since menopause were allowed into the study if they had discontinued the therapy for at least 6 months.

RANDOMIZATION AND INTERVENTION

Eligible participants were given a supply of placebo tablets and asked to return in 4 weeks. Of those who returned, participants who had taken at least 80.0% of the prescribed pills and still met eligibility criteria were randomly assigned in equal proportions to receive 200 mg of isoflavones extracted from soy protein, in 4 tablets of 50 mg each (Novasoy; Archer Daniels Midland Company, Decatur, Illinois), or identical placebo tablets daily for 2 years. Women were instructed to take the study drug in the morning before breakfast. Adherence to study medication was calculated by pill count at each visit. Participants and study personnel who administered interventions and assessed outcomes were masked to treatment assignment.

To ensure sufficient calcium intake, participants whose daily calcium intake was less than 500 mg received supplements of calcium, 1000 mg, plus cholecalciferol, 400 IU, and those who had a daily calcium intake between 500 and 1000 mg received a daily supplement of calcium, 500 mg, plus cholecalciferol, 200 IU.

STUDY OUTCOMES AND FOLLOW-UP

The primary objectives of the study were to determine whether daily intake of 200 mg of soy isoflavones in tablet form prevents the rapid bone loss associated with the initial menopausal years, as measured by the BMD of the lumbar spine, the total hip, and the femoral neck compared with placebo. Secondary objectives included the examination of changes in *N*-telopeptide of type I bone collagen (NTx), menopausal symptoms, vaginal estrogenization, serum lipids, thyrotropin, and thyroid peroxidase autoantibodies. All outcomes were assessed at baseline and 12 and 24 months.

Dual-energy x-ray absorptiometry scans were performed using a Lunar Prodigy Densitometer (GE Lunar Medical Systems, Madison, Wisconsin). Menopausal symptoms were assessed using the Women's Health Questionnaire, which inquires about the frequency of 35 menopausal symptoms.[11] The degree of vaginal estrogenization was determined by calculating the Vaginal Maturation Value (VMV) score from cytology samples obtained from the vaginal wall using Surepath kits (InSure Vision Technologies LLC, Sherman Oaks, California). The VMV is a quantitative analysis reflecting hormonal action on the vaginal epithelium; scores can vary from 0, when only parabasal cells are present, as in the case of atrophic specimens, to 100, for specimens that contain only superficial cells, reflecting a mature specimen.[12] Total isoflavones (ie, genistein, daidzein, and equol) were tested in a fasting spot urine sample using the liquid chromatography tandem mass spectrometry (LC/MS/MS) isotope dilution method.[13] *N*-telopeptide of type I bone collagen was measured in a fasting second-morning urine sample by enhanced chemiluminescence. Triglycerides and high-density lipoprotein cholesterol levels were measured by spectrophotometry, and the low-density lipoprotein cholesterol level was calculated. Thyrotropin and thyroid peroxidase autoantibodies were measured by immunoassay and serum ultrasensitive estradiol via LC/MS/MS; 25-hydroxyvitamin D was measured at baseline and 24 months using an immunochemiluminometric assay (DiaSorin LIAISON; DiaSorin Inc, Stillwater, Minnesota), which measures total 25-hydroxyvitamin D.

Safety measurements included determination of serum comprehensive metabolic panel, complete blood cell count, and mammograms, which were performed at baseline and annually thereafter. If BMD at the spine or hip decreased by 8.0% or more from baseline or between visits or a participant reached a T score of −2.5 or less, as confirmed by a repeat scan, the participant was advised regarding approved therapies for osteoporosis. The Data and Safety Monitoring Committee reviewed unmasked data every 6 months.

STATISTICAL ANALYSIS

The sample size and power calculation was based on testing the primary hypothesis that soy isoflavone tablets prevent bone loss, as assessed by BMD, among women in the early years of menopause. The trial tested the hypothesis that treatment with soy isoflavone tablets maintains BMD values at 2-year follow-up (ie, no additional bone loss) compared with placebo. On the basis of the data provided by the manufacturer, the mean (SD) BMD in women 50 years of age without intervention is 1.149 (0.120) g/cm^2. Women were expected to experience 4.0% to 7.0% bone loss in the first 2 years of menopause.[14-16] Thus, with a sample size of 130 in each group (2-tailed, $\alpha = .05$), the study has a greater than 80% power to detect a 4.0% or greater difference in BMD of the lumbar spine with the assumption that the control group will lose 4.0% to 5.0% bone mass. Assuming a 15.0% attrition rate, the target total sample size was 306. The changes in BMD were compared between the treatment groups by a 2-sample *t* test.

For comparing baseline characteristics between 2 treatment groups, the categorical variables were analyzed via the Pearson χ^2 test or the Fisher exact test if the cell count was less

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than 5; the continuous variables were analyzed via *t* test for differences in means or by Wilcoxon rank sum test for differences in medians. To test the hypothesis that soy isoflavones decrease the number of menopausal symptom incidents in menopausal women, a generalized linear model was fitted to the data using a logarithm canonic link. The number of hot flashes was treated as the dependent variable with Poisson distribution in the model. Treatment vs placebo was included as an indicator variable. Covariates included demographic and pertinent clinical variables (eg, use of antidepressants and/or sleep aids). Statistical significance was considered when the 2-sided test $P < .05$, without multiple testing corrections. All analyses were performed using SAS statistical software, version 9.2 (SAS Institute Inc, Cary, North Carolina).

For vaginal cytologic characteristics, χ^2 tests were used to compare the percentages of basal, intermediate, and superficial squamous cells or VMV between treatment group and controls at a given point of time. For the description of the data, the association of covariates with the VMV at a given point of time was assessed using logistic regression models.

A random-effects model based on an unstructured covariance matrix was used to analyze the effect of the treatment on BMD and other outcomes. Potential confounding factors and effect modifiers discussed herein were adjusted for in the models.

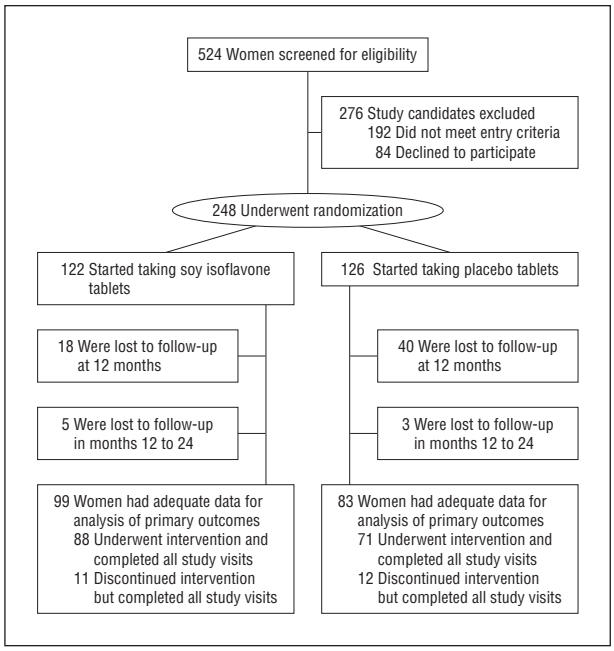

Figure 1. Disposition of participants from screening to study completion. Women responding to advertisements for the study were screened in clinic for study eligibility. Main study exclusion criteria were menopause for more than 5 years, bone mineral density T score less than –2.0, and use of bone active medications.

RESULTS

STUDY PARTICIPANTS AND TREATMENT

Of the 524 women who were screened in clinic, 276 dropped out during the screening process or failed to meet the study eligibility criteria (**Figure 1**). A total of 248 women were eligible and underwent randomization; 122 were assigned to receive soy isoflavone tablets and 126 to receive placebo. Baseline characteristics of the study population have been previously described and were similar between the 2 groups except regarding age (**Table 1**).[10] At baseline, 128 participants (51.6%) had 25-hydroxyvitamin D levels less than 20 ng/mL, 61 (24.6%) in the soy group and 67 (27.0%) in the placebo group. In both treatment arms, more than 60% of participants were white Hispanic. Overall, 66 participants (26.6%) were lost to follow-up during the study, 23 (18.8%) in the soy isoflavone group and 43 (34.1%) in the placebo group ($P = .008$). The demographic characteristics and baseline BMD of participants who were lost to follow-up and those who reached the last study visit did not differ.

The adequacy of masking was assessed by asking participants at their last visit whether they believed they were taking soy isoflavones or placebo tablets. Among the 182 women who finished the study, 172 (94.5%) completed the survey; of the women who responded to that question, 30 of 95 (31.6%) in the soy isoflavone group and 23 of 77 (29.9%) in the placebo group believed they were taking phytoestrogen ($P = .81$).

The mean adherence rate among the participants who continued taking study medication throughout the trial was 88.2% and not significantly different between groups. Among the 182 women who completed the study, 23 (12.6%) stopped taking study medication but completed all or most outcome assessments: 11 (11.2%) in the soy isoflavone group and 12 (15.6%) in the placebo group. Two participants discontinued the use of study medication after a serious adverse event unrelated to the study medication or procedures; the remainder started taking estrogens or soy products or cited personal reasons.

Each 200-mg dose of soy isoflavone contained, on average, 91 mg of genistein and 103 mg of daidzein. The total isoflavone daily dose ranged from 2.05 to 4.50 mg/kg of body weight. Analysis using LC/MS/MS of the total isoflavone content of the isoflavone tablets from the single lot at the beginning and at the end of the study showed 97% and 87% of the label amount, respectively.[10] The placebo tablets contained undetectable isoflavones.

STUDY OUTCOMES

Changes in BMD, NTx, VMV, blood test results, and responses to the Women's Health Questionnaire are given in **Table 2**. During 2 years, no significant differences were found between the women in the soy isoflavone group and in the placebo group regarding changes in spinal BMD (–2.0%; 95% confidence interval [CI], [–2.6% to –1.4%]; and –2.3% [–3.1% to –1.5%], respectively), total hip BMD (–1.2% [–1.6% to –0.7%]; and –1.4% [–2.0% to –0.9%], respectively), femoral neck BMD (–2.2% [–2.7% to –1.6%]; and –2.1% [–2.7% to –1.5%], respectively), or NTx (1.4% [–9.8% to 12.6%]; and –0.2% [–4.9% to 4.5%]; respectively). Results were comparable after those who had discontinued use of the study drug were excluded from the analyses. Subgroup analyses according to race/ethnicity, baseline BMI, estradiol and 25-hydroxyvitamin D serum levels, and whether the women were equol producers or not did not show differences between the groups except among the partici-

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Table 1. Demographic Baseline Characteristics of Study Participants[a]

Characteristic	Group, No. (%) Soy Isoflavone (n = 122)	Placebo (n = 126)
Age, y	53 (3.3)	52 (3.3)[b]
Race or ethnic group, No. (%)		
White Hispanic	76 (62.3)	88 (69.8)
White non-Hispanic	33 (27.0)	23 (18.3)
Black	12 (9.8)	12 (9.5)
Other	1 (0.8)	3 (2.4)
Educational level, y	14.8 (3.1)	14.3 (3.4)
Weight, kg	60.8 (19.8)	62.9 (19.9)
Body mass index[c]	25.9 (3.2)	26.6 (3.3)
Bone mineral density, g/cm^2		
Lumbar spine	1.146 (0.125)	1.132 (0.124)
Total hip	0.990 (0.110)	0.982 (0.104)
Femoral neck	0.940 (0.119)	0.937 (0.100)
T score, No. (%)		
Lumbar spine ≥–1.0	91 (74.6)	84 (66.7)
Lumbar spine <–1.0 to >–2.0	28 (23.0)	35 (27.8)
Total hip ≥–1.0	102 (83.6)	106 (84.1)
Total hip <–1.0 to >–2.0	17 (13.9)	18 (14.3)
NTx, nM BCE/mM CR	50.2 (22.1)	46.9 (20.2)
25-Hydroxyvitamin D, ng/mL	22.6 (7.3)	22.7 (7.4)
Serum estradiol, pg/mL	13.9 (21.1)	18.9 (30.2)
Total isoflavones in urine, pmol/μL	2.0 (6.1)	1.1 (1.5)

Abbreviations: BCE, bone collagen equivalents; CR, creatinine; NTx, *N*-telopeptide of type I bone collagen.

SI conversion factor: To convert estradiol to picomoles per liter, multiply by 3.671.

[a] Data are presented as mean (SD) unless otherwise indicated. Percentages may not total 100 because of rounding.

[b] $P = .04$.

[c] Calculated as weight in kilograms divided by height in meters squared.

pants who had baseline 25-hydroxyvitamin D levels lower than 20 ng/mL; those in the placebo group had a significantly greater decrease in spinal BMD compared with those in the soy group. The mean (SD) change was –0.030 (0.036) g/cm^2 in the placebo group and –0.013 (0.030) g/cm^2 ($P = .03$) in the treatment group or a decrease in spinal BMD of –3.0% and –1.3%, respectively (**Figure 2**).

Overall, 176 women reported 1 or more menopausal symptom at baseline. The most common menopausal symptoms were hot flashes (50.0%), night sweats (37.9%), insomnia (37.1%), loss of libido (37.1%), and vaginal dryness (31.0%). The number of menopausal symptoms was comparable between both groups at baseline and at the end of study except for that of hot flashes. At the end of the study, 48.4% of women in the soy isoflavone group and 31.7% in the placebo group reported having hot flashes ($P = .02$). At baseline, participants in the soy isoflavone and placebo groups had similar VMVs, both in the hypoestrogenic range (ie, <50). No significant changes were found in VMV between baseline and 2-year follow-up in either group. Also, no significant differences were found between groups in changes in total cholesterol, triglycerides, or thyrotropin levels or the number of women with positive thyroid peroxidase autoantibodies test results.

LABORATORY VALUES

Laboratory values remained stable during the study in both groups. At baseline, 47.2% of participants had low but measurable isoflavone concentrations in urine and those participants were equally distributed among treatment arms (Table 1). At study end, mean total urinary isoflavones had increased by 56.5 pmol/μL in the women in the soy isoflavone group and by 2.9 pmol/μL in the placebo group ($P = .001$). A total of 27 women (27.3%) who completed the study in the soy isoflavone group were equol producers, as defined by any measurable amount of urinary equol at the end of the trial.

ADVERSE EVENTS

Almost all participants reported adverse events, which were roughly equally distributed between both groups (**Table 3**). No significant differences were found between groups in the rates of any of the reported adverse effects except constipation. A marginally significantly higher number of women taking soy isoflavones reported constipation compared with women taking placebo (31.2% vs 20.6%, $P = .06$). Vaginal bleeding was reported as an adverse event by 13.9% of women in the soy isoflavone group and 14.3% in the placebo group.

Twelve serious adverse events were reported after randomization: 9 in women assigned to the soy isoflavone group and 3 in women assigned to the placebo group (**Table 4**). Seven women in the soy group and 1 woman in the placebo group reported fractures ($P = .03$). All fractures were associated with a traumatic event and were not considered to be osteoporotic fractures.

COMMENT

In this 2-year randomized trial, we found that tablets containing 200 mg of isoflavones extracted from soy protein administered once daily were not superior to placebo in preventing bone loss or in reducing bone turnover or menopausal symptoms in women in the first 5 years of menopause. Although it has been suggested that individuals who have equol-producing intestinal bacteria are more likely to benefit from soy food consumption than those who do not, our subgroup analyses indicated no benefit in women who were equol producers.[17] Mean 25-hydroxyvitamin D levels at baseline and 24 months were comparable among treatment arms. Post hoc analyses revealed that the rate of spinal bone loss during 2 years was smaller in those receiving soy isoflavones than in those taking placebo only among those participants who had baseline 25-hydroxyvitamin D levels less than 20 ng/mL.

With the exception of age, baseline characteristics of the participants were similar. The age difference was statistically significant but small and unlikely to have any effect on the results. A significant difference was observed in dropouts between the treatment groups; however, this is not an indication that the women taking soy isoflavone tablets were experiencing some type of favorable effect from the intervention because we were unable to objectively document any benefit and a similar

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Table 2. Changes in Primary and Secondary Outcome Measures

	Baseline to Year 1				Baseline to Year 2			
	Soy Isoflavone		Placebo		Soy Isoflavone		Placebo	
Measure	No.	Mean (SE)	No.	Mean (SE)	No.	Mean (SE)	No.	Mean (SE)
Primary outcomes								
Lumbar spine BMD, g/cm^2	102	−0.011 (0.003)	85	−0.011 (0.003)	97	−0.020 (0.003)	80	−0.023 (0.004)
Total hip BMD, g/cm^2	102	−0.006 (0.002)	85	−0.007 (0.002)	97	−0.012 (0.002)	80	−0.014 (0.003)
Femoral neck BMD, g/cm^2	102	−0.008 (0.002)	85	−0.010 (0.004)	97	−0.022 (0.004)	80	−0.021 (0.003)
Secondary outcomes								
NTx, nM BCE/mM CR	98	−0.63 (2.22)	81	1.67 (1.95)	96	1.40 (5.65)	79	−0.23 (2.35)
Vaginal Maturation Value	81	−0.18 (1.97)	71	2.29 (3.31)	76	0.20 (2.53)	66	−1.78 (2.86)
Women's Health Questionnaire	92	0.08 (0.54)	75	−0.37 (0.67)	93	−0.73 (0.54)	74	−0.34 (0.77)
Laboratory values								
Total urinary isoflavones, pmol/μL	97	87.76 (14.95)[a]	84	7.73 (7.25)	97	56.49 (10.44)[a]	86	2.95 (1.47)
Serum estradiol, pg/mL	97	0.88 (1.98)	84	−0.66 (5.17)	97	−3.23 (2.47)	80	−9.18 (3.36)
25-Hydroxyvitamin D, ng/mL		NA		NA	97	2.90 (0.64)	80	2.94 (0.72)
Thyrotropin, mIU/L	96	0.32 (0.08)	81	−0.15 (0.78)	93	0.04 (0.08)	75	−0.61 (0.81)
White blood cells, cells/mm^3	96	−0.42 (0.10)	81	−0.45 (0.11)	93	−0.18 (0.14)	75	−0.15 (0.14)
Neutrophils, cells/mm^3	96	−1.98 (0.79)	81	−0.50 (0.78)	93	−0.57 (0.89)	75	0.49 (0.94)
Lymphocytes, cells/mm^3	96	1.56 (0.71)	81	0.44 (0.72)	93	−0.19 (0.79)	75	−0.84 (0.76)

Abbreviations: BCE, bone collagen equivalents; BMD, bone mineral density; CR, creatinine; NA, not applicable; NTx, *N*-telopeptide of type I bone collagen.

SI conversion factors: To convert estradiol to picomoles per liter, multiply by 3.671; 25-hydroxyvitamin D to nanomoles per liter, multiply by 2.496; and white blood cells, neutrophils, and lymphocytes to number of cells $\times 10^9$ per liter, multiply by 0.001.

[a] $P < .001$.

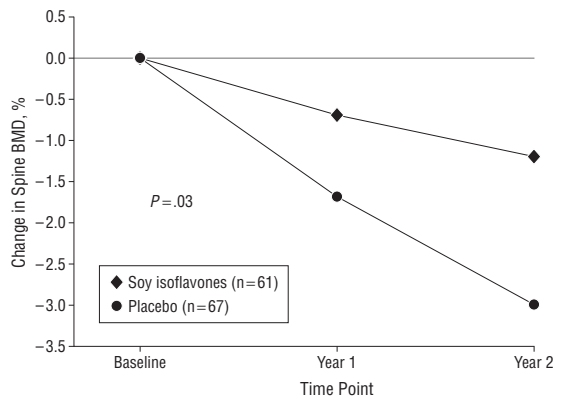

Figure 2. Mean percentage change in spinal bone mineral density (BMD) during the 2-year study period in the participants with baseline 25-hydroxyvitamin D levels less than 20 ng/mL.

Table 3. Number (Percentage) of Women With Adverse Events[a]

	Group, No. (%)	
Adverse Event	Soy Isoflavone (n=122)	Placebo (n=126)
Abdominal bloating	64 (52.5)	54 (42.9)
Headache	54 (44.3)	43 (34.1)
Hair loss	39 (32.0)	43 (34.1)
Dry mouth	35 (28.7)	37 (29.4)
Constipation	38 (31.1)	26 (20.6)[b]
Breast tenderness	31 (25.4)	30 (23.8)
Edema of the lower extremities	19 (15.6)	19 (15.1)
Vaginal bleeding	17 (13.9)	18 (14.3)
Anorexia	21 (17.2)	12 (9.5)
Abnormal mammogram results	9 (7.4)	6 (4.8)
Joint tenderness	6 (4.9)	7 (5.6)
Tenderness of the lower extremities	3 (2.5)	9 (7.1)
Upper respiratory tract infect	7 (5.7)	5 (4.0)
Urinary tract infection	7 (5.7)	5 (4.0)
Hypertension	5 (4.1)	5 (4.0)

[a] Participants with any adverse event: soy isoflavone group, 121 (99.2); placebo group: 122 (96.8).

[b] $P = .06$.

proportion of participants in both arms believed they were in the active arm. Furthermore, hot flashes were more common in the soy group, suggesting a possible antagonistic effect or a strong placebo effect, which has been thoroughly documented in interventions for menopausal symptoms.[18] No significant differences were found between treatment groups in other menopausal symptoms or in vaginal cytologic characteristics.

The type of isoflavone used was similar to the one contained in many soy tablets commonly available in the United States. The study was designed to provide a dose of soy isoflavones about twice the amount of soy isoflavones ingested from food sources in a typical Asian diet and thus to ensure an effective dose.[19] The intervention was considered benign because no abnormalities in laboratory results or significant severe adverse events were reported pertaining to the intervention. Similar to other soy studies,[20] our participants in the soy arm reported more gastrointestinal adverse effects than those taking placebo.

Three recent meta-analyses[21-23] of the effect of soy isoflavones on menopausal bone loss report contradictory results, although these reports did not include all the same original studies, which is a common occurrence.[24] One included studies conducted in Western women only, and 2 reported on studies in Asian and Western women.

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Table 4. Number of Serious Adverse Events

Events	Group, No. (%) Soy Isoflavone (n=122)	Placebo (n=126)
Breast cancer	1 (0.8)	1 (0.8)
Leukemia	1 (0.8)	1 (0.8)
Fracture[a]	7 (5.7)	1 (0.8)[b]

[a] All were considered to be traumatic fractures.
[b] $P = .03$.

Our findings are comparable to the results of 2 recent studies of a lower dose of soy isoflavone (ie, 120 mg) in menopausal women that failed to show any significant effect in turnover markers or BMD of the spine, the total hip, or the femoral neck.[25,26] However, a multicenter Italian trial in menopausal women using the single isoflavone genistein, at approximately half the genistein dose found in our intervention, showed a considerable protective effect on bone. After 2 years, those receiving daily tablets containing 54 mg of genistein had a 5.8% and 5.2% increase in lumbar spine and femoral neck BMD, respectively, and the participants taking placebo experienced a 6.3% and 5.3% loss at those same skeletal sites.[20] The discrepancy in results could be explained by the type of intervention and differences in rates of bone loss among the 2 study populations.

Limitations of our study include a dropout rate that was higher than expected and significantly higher in the placebo group. Also, although a reduced sample size may have caused power loss, the baseline characteristics of participants did not differ largely between those who dropped out and those who remained; thus, the bias due to loss of follow-up was unlikely. The strengths of our study are that the dose of soy isoflavones given to our cohort individuals is the highest tested in a randomized controlled trial, to our knowledge; also, we observed a high adherence rate to the study drug.

The small amount of bone loss in our control group, 2.3% in the lumbar spine and 2.1% in the femoral neck, might have precluded us from detecting any treatment effect. This rate was slightly smaller than that reported in women in the first 4 years of menopause and in the placebo group in the Italian study.[20,27] In white, black, and Asian women, ethnicity, body weight, change in body weight, and smoking status play a significant role in the rate of menopausal bone loss, but risk factors for rapid menopausal bone loss have not been studied in Hispanic women.[28] The participants in our study, who were mostly white non-Hispanic, might have had attributes that made them less susceptible to bone loss. The role of body weight is particularly important because rates of bone loss are 35% to 55% slower in women with higher body weight.[28] Most women in our study were overweight (ie, had a BMI of 20.0 to 29.9). Alternatively, despite having baseline 25-hydroxyvitamin D levels that could be considered insufficient,[29] participants had adequate calcium intake during the trial, which might have contributed to a reduced rate of bone loss.

The accelerated rate of bone loss after menopause is a risk factor for osteoporosis.[14,15] Although the Women's Health Initiative did not address early postmenopausal bone loss, it demonstrated a 24% decreased risk of fractures after an average of 5.2 years of menopausal hormone therapy. Because of concerns regarding the risk of estrogens, a need exists for alternative interventions that could provide the beneficial effects of estrogens in bone and menopausal symptoms without the adverse effects on breast and cardiovascular health. We found that our population of women in the first 5 years of menopause, on average, had low rates of bone loss, and that 200 mg of soy isoflavone tablets taken once daily does not prevent bone loss or reduce bone turnover or menopausal symptoms.

Accepted for Publication: April 18, 2011.
Correspondence: Silvina Levis, MD, University of Miami Miller School of Medicine, PO Box 016960 (D-503), Miami, FL 33101 (slevis@med.miami.edu).
Author Contributions: *Study concept and design:* Levis, Doerge, and Krischer. *Acquisition of data:* Levis, Strickman-Stein, Ganjei-Azar, Xu, and Doerge. *Analysis and interpretation of data:* Levis, Strickman-Stein, Ganjei-Azar, Xu, Doerge, and Krischer. *Drafting of the manuscript:* Levis, Strickman-Stein, and Doerge. *Critical revision of the manuscript for important intellectual content:* Levis, Ganjei-Azar, Xu, Doerge, and Krischer. *Statistical analysis:* Strickman-Stein, Xu, and Krischer. *Obtained funding:* Levis. *Administrative, technical, and material support:* Levis, Strickman-Stein, Ganjei-Azar, Doerge, and Krischer. *Study supervision:* Levis.
Financial Disclosure: None reported.
Funding/Support: National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, grant RO1AR048932-01A1 (Dr Levis).
Role of the Sponsor: The funding agency did not have any role in the design and conduct of the study; the collection, management, analysis, and interpretation of the data; and the preparation, review, or approval of the manuscript.
Additional Contributions: We thank Lisa Rafkin-Mervis, MS, CDE, for her assistance with the study design; Bianca Valme, MPH, for her assistance with the cytology samples; and Ann Herrin, RN, Sylvia Morales, RN, Patricia Bryan, BSN, MPH, Rafael Franjul, and Ashley Barrera for their assistance in the conduct of the study. All were University of Miami employees and supported by the study grant.

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INVITED COMMENTARY

Soy Isoflavones for Prevention of Menopausal Bone Loss and Vasomotor Symptoms

Every woman who lives long enough will go through the menopause transition; approximately 80% will experience hot flashes and night sweats, and approximately 20% will experience sufficient discomfort to seek treatment.[1] Also, women lose bone mass at an accelerated rate of approximately 2% per year during the menopause transition, resulting in increased risk of osteoporosis and fractures later in life.[2]

Estrogen treatment reduces the frequency of hot flashes and night sweats by 60% to 95%, depending on dosage. Estrogen also reduces menopause-associated bone loss and the risk of osteoporotic fractures.[2] Unfortunately, estrogen use is associated with increased risk of venous thromboembolic events, stroke, and cognitive impairment.[3,4] The addition of a progestin to the estrogen regimen, which is required in women with a uterus to prevent the marked increase in risk of uterine hyperplasia and cancer associated with unopposed estrogen, increases the risk of coronary events, stroke, breast cancer, venous thromboembolism, and dementia.[5,6] The increased risk of these adverse effects is small (approximately 1 per 1000 women treated per year). However, approximately 10 million US women are currently using postmenopausal hormone therapy, and even a small increase in risk translates to a large number of adverse outcomes and a major public health effect.

Given this, the search continues for safer alternatives for the treatment of menopausal symptoms and for osteoporosis prevention. In this issue of the *Archives*, Levis et al[7] report the results of the National Institutes of Health–funded Soy Phytoestrogens as Replacement Estrogens (SPARE) trial. Postmenopausal women aged 45 to 60 years who did not have osteoporosis at baseline were randomized to pills delivering 200 mg of soy isoflavones per day or to placebo. After 2 years of follow-up, no differences were observed in bone loss in the lumbar spine, total hip, or femoral neck, but women treated with soy isoflavones reported more hot flashes compared with the placebo group.

The SPARE study was designed to overcome the limitations of many prior trials of soy products, including poor design, small sample size, and short duration. In most respects, the design and conduct of the SPARE study were strong. Entry criteria were clearly defined, change in bone density was measured using the criterion standard method (ie, dual-energy x-ray absorptiometry), the soy isoflavone dosage was relatively large, and participants were

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