Prospective Cohort Study of Soy Food Consumption and Risk of Bone Fracture Among Postmenopausal Women

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Background: Soy consumption has been shown to modulate bone turnover and increase bone mineral density in postmenopausal women. To our knowledge, no published studies have directly examined the association between soy consumption and risk of fracture.

Methods: We examined the relationship between usual soy food consumption and fracture incidence in 24,403 postmenopausal women who had no history of fracture or cancer and were recruited between March 1, 1997, and May 23, 2000, in the Shanghai Women’s Health Study, a cohort study of approximately 75,000 Chinese women aged 40 to 70 years. Usual soy food intake was assessed at baseline and reassessed during follow-up through in-person interviews using a validated food frequency questionnaire. Outcomes were ascertained by biennial in-person interview surveys.

Results: During a mean follow-up of 4.5 years (110,243 person-years), 1,770 incident fractures were identified. After adjustment for age, major risk factors of osteoporosis, socioeconomic status, and other dietary factors, the relative risks (95% confidence intervals) of fracture were 1.00, 0.72 (0.62-0.83), 0.69 (0.59-0.80), 0.64 (0.55-0.76), and 0.63 (0.53-0.76) across quintiles of soy protein intake ($P<.001$ for trend). The inverse association was more pronounced among women in early menopause. The multivariate relative risks (95% confidence intervals) of fracture comparing the extreme quintiles of soy protein intake were 0.52 (0.38-0.70) for women within 10 years of menopause vs 0.71 (0.56-0.89) for late postmenopausal women. Similar results were also found for intake of isoflavones.

Conclusion: Soy food consumption may reduce the risk of fracture in postmenopausal women, particularly among those in the early years following menopause.

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Osteoporosis is a major health threat. Men and women lose bone at a rate of 0.3% to 0.5% per year starting in midlife.1 However, women experience accelerated bone loss at a rate of 3% to 5% per year for about 5 to 7 years following menopause, placing them at a particularly increased risk for fracture.1 It is well known that hormone therapy (HT) prevents postmenopausal osteoporosis and fracture, and this was again confirmed in the recent landmark study, the Women’s Health Initiative trial.2 The Women’s Health Initiative trial, however, also found that HT users had an increased risk of cardiovascular disease and breast cancer that outweighed the benefit of fracture reduction, even in women at high risk of fracture.2 The US Food and Drug Administration3 and new clinical guidelines4 recommend against the use of HT as a first-line therapy for the prevention of osteoporosis in postmenopausal women and place more emphasis on alternatives to HT, including exercise, increasing calcium and vitamin D intake, and other approaches.

Plant-derived estrogens, especially soy phytoestrogens (isoflavones), have attracted considerable attention as a natural substitute for HT in recent years. These compounds are structurally similar to the mammalian estrogen 17β-estradiol, but may exert agonist or antagonist effects on various estrogen target tissues as selective estrogen receptor modulators.5,6 Consumption of soy foods or soy phytoestrogens has had potential beneficial effects on menopausal symptoms,7 cardiovascular disease,5,9 and hormone-related cancers,10,11 although the evidence is not entirely consistent7 and a possible adverse effect of stimulating breast epithelial cell proliferation with high-dose soy supplements has been suggested.12

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Recently, growing evidence has suggested a potential role for soy in preventing postmenopausal bone loss. In vitro studies\(^ {13-15}\) suggest that soy phytoestrogens may favorably affect bone cell activity through estrogen receptor-mediated and non–estrogen receptor–mediated mechanisms, such as the inhibition of tyrosine kinase. Animal studies\(^ {16-17}\) with oophorectomized rat models (a widely used model for postmenopausal osteoporosis) have consistently demonstrated that soy or soy phytoestrogens are effective in preventing oophorectomy-induced bone loss. Several cross-sectional studies\(^ {18-21}\) in postmenopausal women have linked usual dietary soy intake with higher bone mineral density (BMD). Several clinical trials,\(^ {22-33}\) mostly of short duration and with small sample sizes, have also been conducted, using either biomarkers of bone turnover or BMD as the primary outcome, and have yielded inconclusive results. To our knowledge, no study has directly assessed the association between soy consumption and the risk of fracture, a critical end point for interventions aimed at preventing osteoporosis. The Shanghai Women’s Health Study, a large cohort study conducted in a population that has a high, yet wide, range of soy food consumption, provides us with a unique opportunity to evaluate this important hypothesis.

METHODS

The Shanghai Women’s Health Study, formally launched on March 1, 1997, is a population-based, prospective, cohort study of women aged 40 to 70 years living in 7 urban communities of Shanghai. The study was approved by the relevant institutional review boards for human research in the People’s Republic of China and the United States. Of the 81 170 eligible women identified from the Shanghai Resident Registry, 75 221 completed the baseline survey between March 1, 1997, and May 23, 2000, yielding a participation rate of 92.7%. The main reasons for nonparticipation included refusal (2407 women [3.0%]), absence during the study recruitment period (2073 women [2.3%]), and some health-related problems such as mental disorders (1469 women [1.8%]). (Percentages total 100 because of rounding). After exclusion of those who were outside of the study’s age range at the interview, the final cohort consisted of 74 942 women.

The baseline survey was conducted at participants’ homes by trained interviewers using a structured questionnaire. The questionnaire included, among other items, questions on sociodemographic factors, diet and lifestyle habits, menstrual and reproductive history, hormone use, and medical history. Anthropometric measurements, including current weight, height, and circumferences of the waist and hips, were also taken. The cohort was followed up by biennial home visits and linkage with records kept at the Shanghai Cancer Registry, the Shanghai Vital Statistics Registry, and the Shanghai Resident Registry. Follow-up for the cohort was virtually complete. The first follow-up survey was conducted between April 18, 2000, and October 18, 2002, with a response rate of 99.8%. The second follow-up survey was launched on May 20, 2002, and completed on December 31, 2004, with a response rate of 98.7%; only 934 participants (1.3%) were lost to follow-up.

Included in this analysis were postmenopausal women (defined as those in whom menstruation had stopped for at least 12 months, including natural and surgically induced menopause) who had never used HT and reported no history of fracture or cancer at baseline. We further excluded 13 women with an extreme total calorie (energy) intake (<500 or >3500 kcal/d). The final study population comprised 24 403 postmenopausal women.

OUTCOME ASCERTAINMENT

The primary outcomes for the present analysis were incident clinical fractures that occurred after the baseline survey. Fractures of the skull/face, fingers, and toes were excluded. During the 2 biennial in-person follow-up surveys, each participant was asked the following: “Since our last visit, have you suffered any fracture (broken bone) that was confirmed by a physician?” followed by questions on specific details of the fracture, such as the site, the date it occurred, and the hospital of diagnosis.

DIETARY ASSESSMENT

By using a comprehensive quantitative food frequency questionnaire (FFQ), usual dietary intake was assessed twice for most cohort members, first at the baseline survey and then at the first follow-up survey conducted approximately 2 to 3 years after the baseline survey. The FFQ covered virtually all soy foods consumed in urban Shanghai, including soy milk, tofu, soy sprouts, fresh soybeans, and other soy products. During the face-to-face interviews, each participant was first asked how often, on average, during the previous year she had consumed a specific food or food group (the possible responses were daily, weekly, monthly, yearly, or never), followed by a question on the amount consumed in grams per unit of time. For seasonal foods such as fresh beans, participants were asked to describe their consumption during the season(s) when the foods were available on the market. Nutrient intakes were calculated by multiplying the amount of food consumed by the nutrient content per gram of the food, as obtained from the Chinese Food Composition Tables.\(^ {34}\) The isoflavone content of each soy food was derived from published data.\(^ {35}\)

The reproducibility and validity of the FFQ used in this study was assessed in a random sample of 200 Shanghai Women’s Health Study participants.\(^ {36}\) The estimates of nutrient and food intakes derived from the FFQ were moderately correlated with those derived from 24-hour dietary recalls, with the correlation coefficients being 0.59 to 0.66 for macronutrients, 0.41 to 0.59 for micronutrients, and 0.41 to 0.66 for major food groups. The correlation for soy foods was 0.49. The correlations between the 2 FFQs that were completed 2 years apart were 0.48 to 0.51 for macronutrients and 0.37 for soy foods.

STATISTICAL ANALYSIS

Person-years of follow-up were calculated for each participant from the date of the baseline interview to the date of the first fracture, death, cancer diagnosis, or last contact (ie, the date of the second follow-up interview for those who completed 2 follow-up surveys or the date of the first follow-up interview for those who completed only 1 follow-up survey), whichever came first. To better estimate usual dietary intake, we used the mean of intake values reported on the baseline and first follow-up FFQs in the analysis of outcomes that occurred after the first follow-up survey. For outcomes that occurred between the baseline and first follow-up surveys, only information from the baseline FFQ was used. There were 22 566 study participants (92.5%) whose intake values were estimated based on the baseline and first follow-up FFQs and 1837 (7.5%) whose values were based on the baseline FFQ only. Study participants were classified into 5 categories according to quintiles of soy protein or isoflavone intake, with the lowest quintile serv-
ing as the reference group. Incidence rates were calculated by dividing the number of events by the person-years of follow-up in each category. The Cox proportional hazards model was used to compute relative risks (the rate ratios of each specific quintile vs the lowest quintile), and to adjust for potential confounding variables. Variables adjusted for in the multivariate analyses included age, cigarette smoking, alcohol consumption, body mass index (calculated as weight in kilograms divided by the square of height in meters), regular exercise, history of diabetes mellitus, education, family income, and alcohol drinking. Soy protein intake was positively associated with the intake of total calories, protein from other food sources, calcium, and fruits and vegetables.

During a mean follow-up of 4.98 years (110 243 person-years), 1770 incident fractures were identified, including fractures of the wrist (17.6%), arm (15.1%), vertebrae (14.9%), ankle (13.1%), rib (7.0%), and hip (3.3%). 

Table 2 and Table 3 present the relative risks of fracture according to quintiles of soy protein and isoflavone intake, respectively. After adjustment for age and total calorie intake, higher soy protein intake was significantly associated with lower risk of fracture. The inverse association persisted after further adjustment for major risk factors for osteoporotic fractures, socio-economic status, and other dietary factors related to fractures (Table 2). Additional analyses stratified by time since menopause found a more pronounced association among women in early menopause. For women within 10 years of menopause, the multivariate relative risks (95% confidence intervals) were 1.00, 0.68 (0.54-0.86), 0.60 (0.47-0.77), 0.55 (0.42-0.72), and 0.52 (0.38-0.70) across quintiles of soy protein intake (P<.001 for trend), whereas for women who had been menopausal for 10 years or longer, the corresponding relative risks (95% confidence intervals) were 1.00, 0.73 (0.60-0.87), 0.75 (0.62-0.91), 0.70 (0.57-0.86), and 0.71 (0.56-

### RESULTS

The mean age of the study population was 60 years at recruitment, and the mean number of postmenopausal years was 11. The median daily intakes of soy protein and isoflavones were 8.5 g and 38.0 mg, respectively. Table 1 shows the baseline characteristics of the study population by quintiles of soy protein intake. Women with higher soy protein intakes were somewhat more educated and more physically active, and had a slightly higher body mass index and a higher prevalence of diabetes mellitus, compared with those with lower intakes. They did not seem to differ in family income, smoking status, or alcohol consumption. Soy protein intake was positively associated with the intake of total calories, protein from other food sources, calcium, and fruits and vegetables.

| Table 1. Characteristics of the Study Population by Quintiles of Soy Protein Intake* |
|-----------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Quintile of Soy Protein Intake, g/d | Quintile of Soy Protein Intake, g/d | Quintile of Soy Protein Intake, g/d | Quintile of Soy Protein Intake, g/d | Quintile of Soy Protein Intake, g/d |
| Characteristic                      | <4.98 (n = 4880) | 4.98-7.32 (n = 4882) | 7.33-9.77 (n = 4880) | 9.78-13.26 (n = 4880) | ≥13.27 (n = 4881) |
| Age, mean, y                        | 60.2              | 59.5              | 59.4              | 59.5              | 59.6              |
| Level of education                  |                   |                   |                   |                   |                   |
| Elementary school                   | 22.0              | 22.6              | 24.8              | 23.6              | 25.7              |
| Middle school                       | 20.5              | 19.8              | 20.9              | 22.0              | 20.7              |
| High school                         | 16.3              | 13.4              | 12.5              | 13.2              | 13.0              |
| College                             | 10.4              |                   |                   |                   |                   |
| Annual family income, Y             |                   |                   |                   |                   |                   |
| <10 000                             | 20.0              | 19.0              | 19.3              | 20.9              | 22.3              |
| 10 000 to <20 000                   | 28.0              | 29.0              | 30.9              | 34.0              | 39.1              |
| 20 000 to <30 000                   | 28.0              | 29.0              | 30.9              | 34.0              | 39.1              |
| ≥30 000                             | 26.0              | 27.0              | 28.9              | 32.0              | 37.1              |
| Body mass index, mean†              |                   |                   |                   |                   |                   |
| Total calories (energy), kcal       | 1423.4            | 1532.6            | 1610.7            | 1693.6            | 1846.5            |
| Soy protein, g                      | 3.3               | 6.2               | 8.5               | 11.4              | 18.5              |
| Nonsoy protein, g                   | 45.8              | 50.8              | 53.9              | 57.4              | 62.7              |
| Calcium, mg                         | 316.3             | 392.1             | 439.3             | 504.5             | 650.8             |
| Fruits and vegetables, g            | 379.6             | 448.1             | 500.9             | 556.5             | 655.6             |

*Data are given as percentage of each group unless otherwise indicated. Percentages may not total 100 because of rounding.
†Calculated as weight in kilograms divided by the square of height in meters.
The formal test for multiplicative interaction, however, was not significant \(P = .3\). Similar associations were found for intake of isoflavones. Analyses of specific commonly consumed soy foods generally supported the results observed for nutrient analyses.

In this prospective cohort study of postmenopausal women, we found that soy food consumption was associated with a significantly lower risk of fracture, particularly among women in the early years following menopause. This inverse association was independent of major risk factors for osteoporotic fractures and other dietary factors, including intake of calcium, nonsoy protein, fruits, and vegetables.

Soy or soy isoflavones may exert their effects on bone by suppressing bone resorption, while at the same time stimulating bone formation. Soy isoflavones may exert their effects on bone by suppressing bone resorption, while at the same time stimulating bone formation. Soy isoflavones stimulate osteoblastic production of osteoprotegerin, which inhibits the differentiation and activation of osteoclasts and prevents bone resorption. Soy isoflavones also increase the production of insulinlike growth factor 1, a marker known to enhance osteoblastic activity and correlate with bone formation. Soy intake in postmenopausal women has resulted in decreases in urinary excretion of markers of bone resorption (such as deoxypyridinoline and N-telopeptides) and increases in serum markers of bone formation (such as bone-specific alkaline phosphates and osteocalcin).

Observational studies of usual dietary soy intake in relation to BMD, in general, support a bone-sparing effect for soy. Positive associations with BMD at the lumbar spine have been consistently observed among postmenopausal women in Japan\(^{18}\) and the People’s Republic of China.\(^{19}\) Despite the relatively low average soy intake in Western society, one study\(^{20}\) of postmenopausal US women (77.9% white) also found that higher dietary soy isoflavone intake was associated with greater BMD and lower urinary excretion of N-telopeptides. A cross-sectional analysis of data from a US-based multiethnic study of women aged 42 to 52 years found a positive association of soy isoflavone intake with BMD for premenopausal Japanese women, but no association for Chinese women and perimenopausal Japanese women.\(^{21}\) Soy intake in the African American and white women from that study was too low for informative analysis.\(^{21}\)

Supplementation with soy protein and/or isoflavones in postmenopausal women has shown significant protective effects on bone in some clinical trials,\(^{22,25-31}\) but little or no effect in others.\(^{24,32,33}\) In the first published human trial, which included 66 postmenopausal women aged 39 to 83 years, Potter et al\(^{21}\) found that intake of soy protein containing high amounts of isoflavones for 6 months significantly increased bone mineral content.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Quintile of Soy Protein Intake, g/d</th>
<th>(P) Value for Trend</th>
<th>(P) Value for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(&lt;4.98 (n = 4880))</td>
<td>(\geq13.27 (n = 4881))</td>
<td>(\geq13.27 (n = 4881))</td>
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<tr>
<td>No. of follow-ups</td>
<td>9559</td>
<td>9610</td>
<td>9624</td>
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<tr>
<td>Person-years</td>
<td>21.635</td>
<td>22.091</td>
<td>22.232</td>
</tr>
<tr>
<td>No. of cases</td>
<td>459</td>
<td>332</td>
<td>329</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>1.00</td>
<td>0.69 (0.60-0.80)</td>
<td>0.67 (0.58-0.77)</td>
</tr>
<tr>
<td>Age and calorie (energy) adjusted</td>
<td>1.00</td>
<td>0.72 (0.62-0.83)</td>
<td>0.69 (0.59-0.80)</td>
</tr>
<tr>
<td>Multivariate*</td>
<td>1.00</td>
<td>0.75 (0.65-0.87)</td>
<td>0.67 (0.58-0.78)</td>
</tr>
</tbody>
</table>

Table 2. Data for Fracture by Quintile of Soy Protein Intake

Abbreviations: \(P\), relative risk.

*Adjusted for age, body mass index, hours of exercise per week, cigarette smoking, alcohol consumption, history of diabetes mellitus, level of education, family income, season of recruitment, and intakes of total calories, calcium, nonsoy protein, fruits, and vegetables.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Quintile of Soy Isoflavone Intake, mg/d</th>
<th>(P) Value for Trend</th>
<th>(P) Value for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(&lt;21.16 (n = 4881))</td>
<td>(\geq60.27 (n = 4881))</td>
<td>(\geq60.27 (n = 4881))</td>
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<td>No. of follow-ups</td>
<td>9564</td>
<td>9624</td>
<td>9658</td>
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<tr>
<td>Person-years</td>
<td>21.654</td>
<td>22.147</td>
<td>22.136</td>
</tr>
<tr>
<td>No. of cases</td>
<td>450</td>
<td>340</td>
<td>340</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>1.00</td>
<td>0.67 (0.56-0.75)</td>
<td>0.70 (0.60-0.81)</td>
</tr>
<tr>
<td>Age and calorie (energy) adjusted</td>
<td>1.00</td>
<td>0.75 (0.65-0.87)</td>
<td>0.67 (0.58-0.78)</td>
</tr>
<tr>
<td>Multivariate*</td>
<td>1.00</td>
<td>0.75 (0.65-0.87)</td>
<td>0.67 (0.58-0.78)</td>
</tr>
</tbody>
</table>

Table 3. Data for Fracture by Quintile of Soy Isoflavone Intake

Abbreviations: See Table 2.

*Adjusted for age, body mass index, hours of exercise per week, cigarette smoking, alcohol consumption, history of diabetes mellitus, level of education, family income, season of recruitment, and intakes of total calories, calcium, nonsoy protein, fruits, and vegetables.
and BMD of the lumbar spine. In a recent 12-month trial involving 205 women aged 49 to 65 years, Atkinson et al\(^\text{39}\) also found that an isoflavone supplement derived from red clover attenuated bone loss. In contrast, another recently published 12-month trial by Kreijkamp-Kaspers et al\(^\text{39}\) reported no effect of supplementation of soy protein with isoflavones on BMD among 175 postmenopausal women aged 60 to 75 years. However, in their subgroup analysis stratified by the number of postmenopausal years, soy intervention seemed to show positive effects on BMD in women with the most recent onset of menopause (within the first 14 years of menopause), but no effect was found in late postmenopausal women.\(^\text{33}\) Interestingly, we also observed a stronger inverse association between soy consumption and fracture risk among women who were in the early years following menopause (<10 years after menopause), a period during which rapid bone loss occurs. Animal studies\(^\text{10}\) with rat models also showed that soy feeding administered immediately after oophorectomy prevented bone loss, but was less effective when given later. These observations suggest that soy consumption may be particularly beneficial in preventing menopause-related bone loss, but less effective at reversing established bone loss.\(^\text{15}\) The potential impact of timing on the skeletal effects of soy needs to be further addressed in future studies. In addition to timing, other factors may also contribute to soy’s effects.\(^\text{15}\) Of particular importance may be the variations in the metabolism and bioavailability of isoflavones among study subjects. Studies including biomarkers of soy intake and measures of specific isoflavone metabolites (such as equol) may help address this issue.

To our knowledge, this is the first study that has directly assessed the association between soy consumption and the incidence of fracture. The study population is well suited to address this issue because of the high and diverse soy intake. The FFQ used in the study has fairly good validity and reliability. An average of dietary intakes assessed at 2 time points 2 to 3 years apart was used to better estimate usual soy food intake. Other strengths of the study include the population-based prospective study design, the high participation rate, the virtually complete cohort follow-up, the large sample size, and the use of face-to-face interviews. The study results may have some potential implications, especially for women in the early years following menopause.

However, this observational study cannot establish a causal relation between soy consumption and fracture risk reduction. Women in different categories of soy consumption also differed in several other respects, such as baseline disease risk factors and other dietary or lifestyle factors. Although careful adjustment for a wide range of potential confounding variables, including the major risk factors of osteoporosis, dietary and lifestyle factors, sociodemographic factors, and other factors related to domestic violence such as the drinking habit of a spouse, did not appreciably change the results, we could not completely exclude the possibility of residual confounding due to unmeasured or inaccurately measured covariates. Another limitation of the study is that fracture information was collected based on self-reports with no further confirmation by medical record review. Although it is generally believed that self-report for fractures is accurate,\(^\text{87}\) to our knowledge, no validation study has been conducted in this population. Certain fractures, especially vertebral fractures, may have been underreported. On the other hand, we may have included fractures caused by high-impact trauma rather than osteoporosis. Thus, random misclassification in outcome (presumably osteoporotic fractures) may exist, resulting in an attenuated estimation of the soy-fracture association. In addition, our study lacks adequate power to investigate the association of soy with site-specific fractures. Finally, whether the findings of this study on postmenopausal Chinese women in urban Shanghai can be generalized to other populations needs further investigation.

In conclusion, this prospective cohort study provides the first evidence, to our knowledge, for a significant inverse association between soy food consumption and risk of fracture in postmenopausal women, particularly among those in the early years following menopause.

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 Disclaimer: Dr Shu had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analyses.

REFERENCES


