

Motivation

- Men and women lose bone at 0.3%-0.5% per year since midlife
- Bone loss rate is 3%-5% per year for 5 to 7 years following menopause
- WHI study found hormone therapy(HT) increased risk for cardiovascular disease and breast cancer
- Plant-derived estrogens such as soy phytoestrogens(isoflavones) may have beneficial effects on menopausal symptoms
- Recent studies suggest potential role for soy in preventing postmenopausal bone loss

Overview

- Hypothesis: soy consumption is associated with lower risk of fracture
- Study design: prospective cohort of postmenopausal women
- Data collection: in person interviews at baseline and 2 to 3 years followup
- Primary endpoints: incident fracture, time to fracture from baseline
- Primary predictor: soy intake based on food frequency questionnaires

Overview cont'd

- Statistical analysis: Cox PH model, adjust for confounders, test for trend
- Results: relative risks are 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 ($p < 0.001$ for trend).
- Conclusion: soy consumption is inversely associated with risk of fracture among postmenopausal women, especially among those in early years following menopause.

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- Correctly point out this observational study cannot establish causal relationship

Can we improve the analysis?

- Can soy consumption ever be cause for fracture or non-fracture?
- Direct causes of fracture include slip and fall, hit by a car, etc.
- Soy may reduce risk of fracture only through increasing bone density or slowing bone loss
- Have we established association between soy consumption and bone density?
- Implications: subject to serious confounding, time to event is not a good endpoint

Data collection

- Both outcome and soy intake are subject to large recall bias and measurement errors
- This is tough to correct, any suggestions?
- Would be nice to ascertain fracture through medical record
- Would be nice to see a summary of different types of fractures
- Continuous assessment of soy intake over a short period, during different seasons?
- Assessment of FFQ show agreement, not reliability and accuracy

Statistical analysis

- Is time to fracture a good endpoint for soy consumption?
- Categorizing the soy instake has serious consequences
- Arbitrary cutoffs
- Introduce breaks in the risk, same risk for the whole group
- 2 vs 3: $OR=1.01(0.87, 1.89)$, 2 vs 5: $0.998(0.85, 1.17)$
- Bias the results and conclusion if selectively compare to the worst group
- Using median values to replace actual soy instakes for the whol group in trend test

Table 1

Table 1. Characteristics of the Study Population by Quintiles of Soy Protein Intake*

Characteristic	Quintile of Soy Protein Intake, g/d				
	<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	52.9	44.3	41.8	41.2	40.6
Middle school	20.5	22.6	24.8	23.6	25.7
High school	16.3	19.8	20.9	22.0	20.7
≥College	10.4	13.4	12.5	13.2	13.0
Annual family income, ¥					
<10 000	22.0	19.0	19.3	20.9	22.3
10 000 to <20 000	37.0	37.9	37.3	37.6	39.1
20 000 to <30 000	24.9	25.3	26.2	25.1	23.4
≥30 000	16.1	17.8	17.1	16.4	15.2
Body mass index, mean†	24.4	24.5	24.7	24.8	25.1
Regular exercise, mean, h/wk	2.2	2.5	2.8	3.0	3.5
Ever smoked cigarettes	5.8	3.8	4.1	4.0	4.1
Ever drank alcohol	2.6	2.2	2.4	2.7	2.3
Diabetes mellitus	4.5	5.2	6.5	8.3	14.0
Daily intake, 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.

Table 1

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

Variable	Quintile of Soy Protein Intake, g/d					P Value for Trend
	<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)	
No. of follow-ups	9559	9610	9649	9662	9616	NA
Person-years	21 635	22 091	22 232	22 234	22 052	NA
No. of cases	459	332	329	317	333	NA
RR (95% CI)						
Age and calorie (energy) adjusted	1.00	0.69 (0.60-0.80)	0.67 (0.58-0.77)	0.63 (0.54-0.73)	0.63 (0.54-0.74)	<.001
Multivariate*	1.00	0.72 (0.62-0.83)	0.69 (0.59-0.80)	0.64 (0.55-0.76)	0.63 (0.53-0.76)	<.001

Abbreviations: CI, confidence interval; NA, data not applicable; RR, 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 1

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

Variable	Quintile of Soy Isoflavone Intake, mg/d					P Value for Trend
	<21.16 (n = 4881)	21.16-32.39 (n = 4881)	32.40-44.31 (n = 4880)	44.32-60.26 (n = 4880)	≥60.27 (n = 4881)	
No. of follow-ups	9564	9624	9648	9658	9602	NA
Person-years	21 654	22 147	22 288	22 136	22 018	NA
No. of cases	450	340	312	340	328	NA
RR (95% CI)						
Age and calorie (energy) adjusted	1.00	0.72 (0.63-0.83)	0.65 (0.56-0.75)	0.70 (0.60-0.81)	0.65 (0.56-0.76)	<.001
Multivariate*	1.00	0.75 (0.65-0.87)	0.67 (0.58-0.78)	0.72 (0.61-0.84)	0.65 (0.55-0.78)	<.001

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.