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A population-based cohort study on phytoestrogen intake and bone loss in Chinese early post-menopausal women

Key Messages

This study has found that, in post-menopausal women the habitual soy intake has a beneficial effect on bone mass, particularly after the initial years of dramatic hormonal change. At least 40 mg of soy isoflavones per day seem to be necessary to exert the effect but it is probable that a higher intake is required to achieve optimal effects on bone health. At least one glass of soy milk daily and a small bowl of tofu or their equivalent would be beneficial. As osteoporosis is a major public health problem in Hong Kong and Asia, lifestyle advice should include recommendation of a higher consumption of soy.

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Introduction

It has been hypothesised that dietary soy may have a beneficial effect on bone health. Data from rodent studies are supportive of such a hypothesis, but human studies are limited and have shown inconsistent results.

Soy is part of the traditional diet in Asian populations and is their major source of isoflavones, a form of phytoestrogen. The limited published data on the soy-bone relationship in these populations have generally revealed a positive role for phytoestrogens in bone health.[1-4]

This study aimed to investigate the relationship between phytoestrogen consumption (intake of total isoflavones) and bone changes in early post-menopausal women. The hypothesis to be tested is that high dietary levels of isoflavonoid phytoestrogens reduce bone loss in early post-menopausal women.

Methods

This study was conducted from October 1999 to June 2002. Four hundred and fifty-four early post-menopausal women were recruited from the community using stratified-cluster sampling based on the three housing types (public, private, and home ownership) using a 3:2:1 ratio, in Shatin. Housing estates and the housing blocks within the estates were randomly selected from these three types of housing. A letter introducing the study was sent to all flats in the selected blocks before a door-to-door interview was conducted. Each flat was visited up to three times. Women who were within the specified age range and years since menopause were screened for eligibility. The response rate among the potentially eligible women recruited door-to-door was 75.3%. To increase the response rate, invitation letters were placed in mailboxes. Among the 144 eligible women who responded, 136 were successfully recruited into the study.

An eligible subject was defined as a post-menopausal Chinese woman who had undergone natural menopause within the previous 12 years, and did not have any of the following features: surgical menopause, on exogenous oestrogens use for at least 3 months, on a special diet; a history of malabsorption disorders; surgical removal of the stomach or intestines; cancer, a history of metabolic diseases; on medication leading to bone loss. The eligible women were invited to attend structured face-to-face interviews and bone mineral density (BMD) and anthropometric measurements. Data collection was conducted at baseline, 9 months, and 18 months. The assessment of total isoflavone consumption was based on (a) previously validated semi-quantitative food questionnaire, r=0.68, and (b) 24-hour urinary excretion of isoflavones by a high-performance liquid chromatography method.[5] The dietary questionnaire was administered by an interviewer trained in dietary assessment. Dietary recall was aided by the structured questionnaire, food pictures, and models of household containers. Subjects were asked about the usual intake in the previous 12 months. Quantification of total isoflavones was based on published information.[5]

Table 1. Mean±SD soy isoflavone intake (mg/d) and mean±SD bone mineral density (BMD)/bone mineral content (BMC) values at various sites by soy isoflavone intake quartiles

Intake quartile	No.	Intake (mg/day)	BMD (g/cm²)				BMC (g)	
			Spine	Femoral neck	Trochanter	Intertrochanteric	Total hip	Total body
Years since menopause <4								
1	64	3.03±1.82	0.842±0.115	0.689±0.107	0.596±0.101	0.979±0.142	23.1±3.92	1658±247
2	62	841±1.59	0.865±0.122	0.685±0.086	0.590±0.085	0.959±0.130	23.6±3.96	1651±230
3	68	15.79±2.65	0.861±0.153	0.684±0.106	0.601±0.104	0.970±0.144	23.5±4.45	1658±284
4	75	41.84±23.25	0.857±0.126	0.706±0.097	0.608±0.087	0.984±0.116	24.0±3.71	1667±224
P value for trend test		<0.001	0.601	0.335	0.356	0.683	0.195	0.807
Years since menopause ≥4								
1	49	3.03±1.72	0.807±0.121	0.653±0.103	0.564±0.096*	0.912±0.148†	22.0±3.93†	1528±248†
2	52	8.33±4.48	0.779±0.126	0.655±0.103	0.572±0.109	0.927±0.153	22.5±4.19	1512±230
3	46	15.30±3.03	0.847±0.125	0.677±0.083	0.598±0.081	0.962±0.111	23.6±4.12	1592±220
4	38	43.55±28.44	0.821±0.140	0.679±0.105	0.606±0.106	0.983±0.149	24.2±4.43	1635±245
P value for trend test		<0.001	0.181	0.126	0.022	0.01	0.006	0.015

* P<0.1 from *t*-test comparing mean BMD values between Q1 and Q4 intake groups
† P≤0.05 from *t*-test comparing mean BMD values between Q1 and Q4 intake groups

Table 2. Multivariate analysis of the association between soy isoflavones and years since menopause in women 4 years since menopause (n=185)

	β	SE of β	P value	R^2
BMD (g/cm²)				
Spine				
Soy isoflavone intake quartile	0.0086	0.0081	0.291	0.6
Body weight	0.0054	0.001	<0.001	14.7
Years since menopause	-0.0051	0.0052	0.323	0.5
Total R^2				15.9
Femoral neck				
Soy isoflavone intake quartile	0.0083	0.0062	0.18	1
Body weight	0.0044	0.0007	<0.001	16.7
Years since menopause	-0.0052	0.0039	0.183	1
Total R^2				18.6
Trochanter				
Soy isoflavone intake quartile	0.013	0.006	0.032	2.5
Body weight	0.0048	0.0007	<0.001	19.7
Years since menopause	-0.0058	0.0038	0.128	1.3
Total R^2				22.9
Intertrochanteric				
Soy isoflavone intake quartile	0.0209	0.0085	0.015	3.3
Body weight	0.0074	0.001	<0.001	22.6
Years since menopause	-0.0054	0.0054	0.314	0.6
Total R^2				25.8
Total hip				
Soy isoflavone intake quartile	0.0168	0.0069	0.016	3.2
Body weight	0.0064	0.0008	<0.001	24.3
Years since menopause	-0.0061	0.0044	0.166	1.1
Total R^2				27.6
Total body				
Soy isoflavone intake quartile	0.0109	0.0057	0.059	2
Body weight	0.0026	0.0007	<0.001	7.2
Years since menopause	-0.0063	0.0037	0.084	1.7
Total R^2				10.7
BMC (g)				
Total hip				
Soy isoflavone intake quartile	0.629	0.235	0.008	3.8
Body weight	0.253	0.028	<0.001	30.7
Years since menopause	-0.171	0.15	0.255	0.7
Total R^2				33.8
Total body				
Soy isoflavone intake quartile	31.661	13.776	0.023	2.9
Body weight	13.43	1.65	<0.001	27
Years since menopause	-16.4	8.767	0.063	1.9
Total R^2				30.4

Bone mass measurements were performed by means of the dual energy X-ray densitometry (Hologic 4500A; Hologic, Inc., Bedford, MA, US) at the lumbar vertebrae L2 to L4, the left hip, and the total body. The measurements were repeated at 9 months and 18 months.

Table 3. Percentage change of bone mineral density (BMD)/bone mineral content (BMC) between baseline and 18-month follow-up by soy isoflavone intake quartile

Intake quartile	No.	Intake (mg/day)	Mean % change in	
			Spine	Femoral neck
Years since menopause <4 (n=200)				
Soy isoflavone intake (baseline)				
1	42	3.08±1.84	-1.09±4.07	-1.18±3.36*
2	46	8.34±1.60	-1.45±3.00	-1.52±4.09
3	52	15.80±2.63	-1.77±2.86	-2.69±3.30
4	60	40.82±23.17	-1.21±3.66	-2.23±3.35
Total	200	18.92±19.70	-1.38±3.40	-1.97±3.54
P value (ANOVA)		<0.001	0.769	0.153
P value (ANCOVA)‡			0.615	0.07
Soy isoflavone intake (mean from 0, 9, 18 months)				
1	43	4.19±1.76	-1.14±4.17	-1.85±3.96
2	40	10.32±1.59	-1.23±2.77	-2.07±2.58
3	58	17.83±2.76	-2.06±3.21	-1.66±3.76
4	59	38.72±14.82	-1.01±3.34	-2.28±3.63
Total	200	19.56±15.66	-1.38±3.40	-1.97±3.54
P value (ANOVA)		<0.001	0.345	0.813
P value (ANCOVA)‡			0.446	0.656
Years since menopause ≥4 (n=140)				
Soy isoflavone intake (baseline)				
1	33	2.85±1.78	-0.66±4.80	-2.51±3.28
2	43	8.23±1.41	0.35±3.17	-1.77±3.86
3	34	15.72±3.15	-0.59±2.23	-1.32±3.97
4	30	41.49±21.72	0.44±3.08	-1.16±2.61
Total	140	15.91±17.38	-0.10±3.43	-1.70±3.52
P value (ANOVA)		<0.001	0.391	0.414
P value (ANCOVA)‡			0.435	0.18
Soy isoflavone intake (mean from 0, 9, 18 months)				
1	33	4.65±1.98	-0.30±5.25	-2.47±3.68
2	44	10.79±1.56	-0.10±2.85	-1.70±3.97
3	29	17.24±2.40	-0.15±2.64	-1.33±3.47
4	34	38.96±17.96	0.15±2.49	-1.29±2.72
Total	140	17.52±15.67	-0.10±3.43	-1.70±3.52
P value (ANOVA)		<0.001	0.96	0.503
P value (ANCOVA)‡			0.999	0.325

* P<0.05 by multiple range test comparing with 3rd quartile
† P<0.05 by multiple range test comparing with 4th quartile
‡ ANCOVA: adjusted for baseline body weight, age, BMD/BMC, years since menopause, months of follow-up, education, mean calcium intake over follow-up, mean hours per week on stand/walk/load over follow-up period

Results

The mean age of the study subjects was 55.1 (standard deviation [SD], 3.57) years, and the mean number of years since menopause was 3.76 (SD, 2.98). Approximately 41% of the study population were at least 4 years post-menopausal. About two thirds of the study subjects were housewives. Only 2.2% of the women smoked, and 4% were occasional alcohol drinkers. The daily mean intakes of soy protein, isoflavones, and calcium were 7.9 g, 17.3 mg, and 567 mg, respectively.

We observed little difference in BMD values among different soy intake quartiles in women within the first post-menopausal year, but among women of ≥4 years post-menopausal, we noted higher BMD values at the trochanteric and intertrochanteric sites, as well as higher total hip and total body BMD values with increasing soy isoflavones intake quartiles (P<0.05 from tests for trend). The differences in BMD values between the first and fourth intake quartiles ranged from 4 to 8% at the various sites of the hip, and 1.7 % for the spine. We also observed statistically significant trends of association between hip BMD as well as total hip or total body bone mineral content (BMC) values and soy isoflavone intake quartiles (Table 1). Soy isoflavone intake, together with body weight and years since menopause, explained about one quarter of the variation in trochanteric and total hip BMD; and about one third of that of total hip and body BMC. Soy protein alone explained 3 to 4% of the total BMD or BMC variation in these regions (Table 2). 340 women were retained for an 18-month follow-up, and we noted a generally smaller decline in BMD/BMC in subjects belonging to the highest quartile of soy isoflavone intake, but the differences of bone changes among different quartiles were not statistically significant (Table 3). Among later menopausal women, those belonging to the higher intake quartiles showed a lower risk of having ≥1.5% bone loss, but the reduction in odds ratio was not statistically significant (data not shown).

Discussion

Our cross-sectional analysis showed little association between soy intake and bone mass in women within the first 4 years after menopause, but we did observe a positive association between soy intake and hip as well as total body BMD and BMC in women in later menopausal years. Our 18-month follow-up study also found a trend in the

BMD (g/cm²) between 18-month and baseline				BMC (g)	
Trochanter	Intertrochanteric	Total hip	Total body	Total hip	Total body
-1.48±3.22	-1.35±2.75	-1.24±2.43	-1.81±2.21*	-0.28±3.48*	-0.31±3.84
-0.69±4.58*	-0.44±3.16*	-0.65±2.71*	-1.62±2.35*	-0.03±3.52*	0.01±3.02
-2.26±3.79	-1.84±3.81	-1.99±3.20	-3.05±2.85†	-1.80±3.92†	-0.85±4.50
-1.09±2.74	-0.96±2.90	-1.13±2.17	-1.77±2.21	-0.39±3.43	-0.09±3.27
-1.38±3.63	-1.15±3.21	-1.27±2.67	-2.08±2.48	-0.64±3.64	-0.31±3.68
0.162	0.169	0.092	0.011	0.054	0.65
0.313	0.148	0.084	0.018	0.04	0.891
-1.97±2.94	-1.37±3.14	-1.47±2.35	-1.65±1.90*	-1.03±3.34	-0.38±3.47
-1.11±3.31	-0.71±2.63	-0.86±2.21	-2.80±2.65†	-0.01±2.91	0.10±3.44
-1.21±4.57	-1.25±3.67	-1.31±3.27	-2.21±2.81	-0.55±3.72	-0.94±4.56
-1.31±3.25	-1.20±3.17	-1.35±2.55	-1.77±2.30	-0.86±4.19	0.08±2.96
-1.38±3.63	-1.15±3.21	-1.27±2.67	-2.08±2.48	-0.64±3.64	-0.31±3.68
0.68	0.797	0.746	0.119	0.585	0.421
0.84	0.622	0.698	0.073	0.301	0.631
-0.99±5.08	0.13±3.44	-0.49±3.33	-1.50±2.39	-0.03±3.39	1.72±3.27
-0.37±3.16	-0.21±2.70	-0.42±2.22	-0.82±1.98	-0.43±4.14*	1.46±3.33
-0.14±3.74	0.26±3.41	-0.41±2.62	-1.07±1.83	1.33±4.25	1.33±2.68
-0.98±2.61	-0.83±2.93	-0.71±2.06	-0.74±1.93	-0.26±3.15	1.52±4.00
-0.59±3.73	-0.15±3.10	-0.50±2.56	-1.03±2.04	0.13±3.83	1.50±3.29
0.717	0.514	0.964	0.416	0.202	0.97
0.732	0.575	0.952	0.625	0.158	0.677
-1.19±4.78	-0.21±3.50	-0.70±3.20	-1.18±2.52	-0.50±3.49	1.55±3.02
0.24±3.92	0.19±3.10	-0.13±2.58	-0.85±1.91	0.71±4.54	1.86±3.19
-0.92±3.08	-0.16±2.69	-0.50±2.39	-1.11±1.57	0.20±2.86	1.37±3.42
-0.78±2.62	-0.53±3.12	-0.77±1.97	-1.03±2.10	-0.07±3.91	1.09±3.65
-0.59±3.73	-0.15±3.10	-0.50±2.56	-1.03±2.04	0.13±3.83	1.50±3.29
0.345	0.791	0.685	0.904	0.576	0.777
0.286	0.954	0.754	0.453	0.573	0.824

association between higher mean soy intake and smaller bone loss during the follow-up period. However, the association was non-significant as the 18-month changes in the later post-menopausal (beyond 4 years) women were rather small. In this study, women belonging to the highest quartile of soy isoflavone intake had a mean intake of about 40 mg per day.

The stronger effect of soy on hip rather than spine BMD is intriguing. However, as trabecular bone is markedly affected during oestrogen decline, it is possible that the moderate level of soy intake may be inadequate to exert a protective effect at the spine which is composed of mostly trabecular bone. The levels at which soy isoflavones benefit bone health seem to vary with age and stages of menopause.

This study is one of the few population-based cross-sectional studies, and the first longitudinal study in an Asian population, to test the role soy isoflavone intake plays in bone mass and bone changes. However, the follow-up was relatively short (18 months), so the milder effect of soy isoflavones could be masked by other stronger determinants such as body weight and years since menopause. Longer trials are needed to determine the optimal level of soy isoflavone required and the maximum benefit that can be obtained.

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