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Adolescent and adult soy intake and risk of breast cancer in Asian-Americans

Anna H.Wu[1,3], Peggy Wan[1], Jean Hankin[2], Chiu-Chen Tseng[1], Mimi C.Yu[1] and Malcolm C.Pike[1]

[1]Department of Preventive Medicine, University of Southern California, Keck School of Medicine, Los Angeles, CA, USA and [2]J.Hankin, Cancer Research Center, University of Hawaii, Honolulu, Hawaii

[3]To whom correspondence should be addressed
Email: annawu@hsc.usc.edu

The association between soyfood intake and breast cancer risk is controversial. Most of the epidemiologic studies published on this topic in the 1990s were not designed to specifically address this question. We conducted a population-based, case-control study of breast cancer among Chinese, Japanese and Filipino women in Los Angeles County to further investigate the role of soy. Our primary objective was to quantify breast cancer risks associated with intake of soy during adolescence and adult life among Asian-American women. During 1995–1998, we successfully interviewed 501 breast cancer patients and 594 control subjects. Intake of soy among Asian-Americans is still relatively high; the median intake was 12 mg isoflavones/day, approximately one-third of that reported in a recent study in Shanghai, China. The risk of breast cancer was significantly inversely associated with soy intake during adolescence and adult life. After adjusting for age, specific Asian ethnicity, education, migration history and menstrual and reproductive factors, women who reported soy intake at least once per week during adolescence showed a statistically significantly reduced risk of breast cancer. There was also a significant trend of decreasing risk with increasing soy intake during adult life. When we considered soy intake during both adolescence and adult life, subjects who were high-soy consumers during both time periods showed the lowest risk (OR = 0.53, 95% CI = 0.36–0.78) compared with those who were low consumers during both time periods. Risk of breast cancer was intermediate among subjects who were high-soy consumers during adolescence and low-soy consumers during adult life (OR = 0.77, 95% CI = 0.51–1.10). Based on a relatively small number of subjects, the risk did not appear to differ between those who were low consumers during adolescence and high consumers during adult life. Results remained similar after adjustment for other potential confounders including other dietary and non-dietary risk factors for breast cancer. These results show that high soy intake in childhood in Asian-Americans is associated with reduced breast cancer risk. Risk may be further reduced by intake as an adult.

Introduction

Since Lee *et al*. (1,2) first reported a reduced risk of breast cancer in premenopausal women in relation to high soy intake in Singapore, there has been tremendous interest to further investigate the possible role of soy in reducing breast cancer risk. During the 1990s, two prospective studies (3,4) and four case-control studies (5–8) provided mixed results on dietary soy intake and breast cancer risk (see ref. 4, summary). These epidemiologic studies on soy and breast cancer were not specifically designed to study the role of soy and the assessments of soy intake were crude and incomplete, offering limited information on dose–response relationships. In addition, only some of the studies considered potential confounders in their analysis. In 2001, large case-control studies conducted in Shanghai, China (9,10) and among non-Asians in the San Francisco Bay Area (11) were published, providing additional information on soy intake and risk of breast cancer. Both studies were well designed, carefully assessed the intake of soy and other dietary factors, and considered both dietary and non-dietary potential confounders in their analyses. Intake of soy during adolescence was also considered in the Shanghai study but not in the San Francisco study. In Shanghai, the risk of breast cancer was reduced in association with reported soy intake. Soy intake during adolescence conferred a strong significant protective effect (10) and there was a non-significant reduced risk associated with adult soy intake (9). Risk of breast cancer was not associated with intake of soy in the San Francisco study (11). However, daily median intake of soy was substantially lower (1.6 mg of isoflavones) among the San Francisco Bay Area non-Asians than in the Chinese in Shanghai (33 mg of isoflavones).

Since 1995, we have been conducting a case-control study of breast cancer among Asian-Americans in Los Angeles County to investigate further the role of soy and breast cancer. We report below, results from the first 501 cases and 594 controls interviewed on soy intake during adolescence and adult life. Intake of soy among Asian-Americans is intermediate between those of Chinese in Shanghai and non-Asians in the San Francisco Bay Area. This study offers some further insights regarding doses of soy intake in human diets and timing of exposure in relation to breast cancer risk.

Abbreviations: BMI, body mass index; CI, confidence intervals; OR, odds ratio.

Materials and methods

This population-based, case-control study includes women who were identified as Chinese, Japanese or Filipino, between the ages of 25 and 74 years at the time of diagnosis of an incident breast cancer on or after January 1, 1995. Cases were identified through the Los Angeles County Cancer Surveillance Program, a population-based cancer registry that is a member of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program and the statewide California Cancer Registry. Of the 871 Chinese, Japanese and Filipino women identified, 523 were interviewed (22 were partially complete and excluded from the final analysis), 244 declined to be interviewed (198 patients declined, 46 physicians declined to give permission to contact the patient), 11 were deceased and 93 could not be located or had moved outside of Los Angeles County. 594 controls were selected from the neighborhoods where cancer cases resided at the time of diagnosis using a well-established, standard algorithm to identify neighborhood controls that the USC Epidemiology Program have used in numerous case-control studies. Controls were frequency-matched to cases on specific Asian ethnicity and age (±5 years). On average, a suitable control was identified after walking 61

Table I. Characteristics of cases and controls, Los Angeles County (percents are shown)

	All subjects		Chinese		Japanese		Filipinos	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
n	501	594	160	228	146	175	195	191
Age								
⩽39	9.8	15.5	10.10	18.4	7.5	13.7	11.3	13.6
40–49	31.9	36.2	38.8	44.7	21.9	27.4	33.8	34.0
50–59	28.9	24.4	24.4	20.6	34.2	26.9	28.7	26.7
60–69	20.8	15.5	19.4	9.6	24.7	20.0	19.0	18.3
70+	8.6	8.4	7.5	6.6	11.6	12.0	7.2	7.3
Mean age	52.9	50.8[a]	52.0	48.5[a]	55.5	53.2	51.7	51.2
Birthplace								
US born	25.1	27.4	13.8	13.6	68.5	72.0	2.1	3.1
Non-US born	74.9	72.6	86.3	86.4	31.5	28.0	97.9	96.9
Mean year in US[b]	18.6	17.2	17.3	15.4	30.0	25.4	16.8	16.9
Mean age at migration[b]	33.0	32.5	33.9	33.2	22.0	23.5	35.0	34.2
Education								
⩽High school	22.4	19.5	32.5	29.8	22.6	17.7	13.8	8.9
Some college	20.0	27.1	16.9	22.8	32.9	36.6	12.8	23.6
College graduate	40.0	37.9	33.8	30.3	28.8	30.9	53.8	53.4
>College	17.6	15.5	16.9	17.1	15.8	14.9	19.5	14.1[a]
Age at menarche								
⩽11	17.1	15.9	6.4	7.9	25.5	25.1	19.6	16.8
12–13	50.0	53.1	51.9	48.2	49.0	57.1	49.2	55.3
14+	32.9	31.0	41.7	43.9	25.5	17.7	31.2	27.9
Mean age	13.0	13.0	13.4	13.4	12.7	12.5	13.0	12.8
Pregnancy								
Never	21.9	12.0	17.0	8.3	20.5	17.7	27.1	11.1
Yes, no livebirth	4.4	4.9	2.5	3.1	5.5	6.9	5.2	5.3
1+ livebirth	73.6	83.1	80.5	88.6	74.0	75.4	67.7	83.7
Mean no. livebirths[c]	1.88	2.32[a]	1.94	2.19	1.73	1.80	1.94	2.94[a]
Current BMI+								
Q1 (low)	28.7	25.3	35.7	35.7	32.6	22.5	19.8	15.4
Q2	20.8	25.1	24.7	27.1	22.9	26.0	16.0	21.8
Q3	22.5	24.2	17.5	19.0	18.8	25.4	29.4	29.3
Q4	28.0	25.4	22.1	18.1	25.7	26.0	34.8	33.5
Mean BMI	23.4	23.3	22.6	22.3	23.0	23.7	24.3	24.0

[a]$P<0.05$, comparison between cases and controls + current BMI was calculated as weight in kilograms divided by square of height in meters. The quartile cut points are selected based on all control subjects (⩽20.9, 20.9–22.8, 22.9–25.0, >25.0).
[b]Among non-US born.
[c]Among all women.

houses. In 151 instances, a first suitable control refused to participate and a second or later control was identified.

In-person interviews were conducted using a standardized, structured questionnaire that covered demographic characteristics and migration history, menstrual and reproductive history, body size, physical activity and diet history. The diet questionnaire was developed in collaboration with Dr Jean Hankin at the University of Hawaii and was modeled after the validated diet instrument used in the Multiethnic Cohort Study being conducted in Hawaii and Los Angeles (12,13). Dietary intake during the year prior to cancer diagnosis (for cases) and interview (for controls) was determined. Soy intake during adult life was estimated based on the intake pattern of 14 foods that are rich in soy [miso soup or soups with tofu, tofu with pork or beef, tofu with chicken, fish or shellfish, tofu and vegetables (no meat), fresh green soy beans, dried soy beans, natto, fresh tofu, fried tofu, dried or pressed tofu, Chinese vegetarian meats, western vegetarian meats, soymilk and soy bean desserts]. The frequency of intake and the usual amounts consumed were asked. The assessment of soy intake during adolescence (between ages 12 and 18) was crude, based on the usual frequency of intake of tofu (did not eat, less than once a month, two to three times per month, one to three times per week, four to six times per week, daily or more often) (this will be referred to hereafter as adolescent soy intake). Using the Hawaii Food Composition Database (13), total intake of isoflavones (mg per day) during adult life was estimated based on total combined levels of daidzein, genistein and glycitein measured in these soy foods.

Data analyses were based on 501 cases and 594 controls. Odds ratios (ORs; relative risk estimates) and their corresponding 95% confidence intervals (95% CIs) and two-sided *P* values were calculated by conditional logistic regression analysis, with matched sets defined jointly by age (⩽39, 40–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70+) and specific Asian ethnicity (Chinese, Japanese, Filipino) (14). All regression models also included as covariates, education (less than high school, high school, some college, college graduate, graduate), birthplace (US born, non-US born), age at menarche (<12, 12–13, 14–15, 16+), parity (never pregnant, ever pregnant but no live births, 1+ live birth) (categorical), current body mass index (BMI) (in quartiles), menopausal status (premenopausal, postmenopausal) and use of menopausal hormones (never, former, current). Quartile cut points for isoflavone intake were selected based on intake of isoflavones among all control women. Isoflavone density expressed as intake per 1000 kcal was used in all data analyses as a means for adjusting for total reported energy intake. Quartile ORs were computed by defining the lowest quartile of intake as the referent category. We also examined separately the risk estimates in relation to specific soy foods, and we considered various models to adjust for other potential confounders. These are described in the results. All *P* values quoted are two-sided.

Results

Table I shows select demographic and lifestyle characteristics of 501 cases and 594 controls. Cases were, on average, 2 years older than controls, but were similar in terms of birthplace, education, age at menarche and BMI. Cases were significantly more likely to be nulliparous and had fewer livebirths.

Table II shows the mean daily intake of soy (in mg of isoflavones among control subjects) by Asian ethnicity and

Table II. Adult mean daily intake of soy (mg isoflavones) (±standard deviation) among control women, by Asian ethnicity and migration status [numbers are shown in parentheses]

	All subjects	Chinese	Japanese	Filipino
All subjects	18.7 ± 22.1	26.8 ± 26.8 [228]	18.4 ± 17.4 [175]	9.3 ± 15.0 [191]
By birthplace				
US born	14.3 ± 14.3	11.6 ± 10.3 [31]	15.3 ± 15.3 [126]	7.5 ± 6.2 [6]
Non-US born	20.4 ± 24.3	29.2 ± 27.8 [197]	26.6 ± 20.0 [49]	9.4 ± 15.2 [185]
By years lived in the US among the Non-US born				
21+ years	17.5 ± 24.5	25.7 ± 29.3 [51]	22.7 ± 15.1 [27]	9.3 ± 21.0 [69]
11–20 years	20.7 ± 23.0	27.4 ± 26.8 [74]	34.2 ± 21.5 [15]	9.6 ± 10.4 [62]
⩽10 years	23.2 ± 25.1	33.7 ± 27.4 [72]	25.4 ± 30.3 [7]	9.1 ± 10.6 [54]

Table III. Risk of breast cancer in association with intake of soy during adolescence and adult life, Los Angeles County

		No. cases	No. controls	Adjusted OR[a] (95% CI)	Adjusted OR[b] (95% CI)
Tofu intake during adolescence					
Less than monthly		171	148	1.00	1.00
1–3 times/month		79	89	0.75 (0.48–1.15)	0.73 (0.47–1.14)
1–3 times/week		189	270	0.56 (0.38–0.82)	0.62 (0.42–0.92)
4+ times/week		55	85	0.51 (0.31–0.84)	0.65 (0.38–1.10)
P trend				0.002	0.04
Adult intake of isoflavone (mg/1000 kcal)					
⩽1.79		148	130	1.00	1.00
>1.79–6.24		125	147	0.76 (0.53–1.09)	0.85 (0.59–1.24)
>6.24–12.68		124	150	0.69 (0.46–1.02)	0.80 (0.54–1.20)
>12.68		104	166	0.51 (0.33–0.78)	0.61 (0.39–0.97)
P trend				0.003	0.04
Adolescent tofu	Adult isoflavone intake[c]				
Low	Low	190	182	1.00	1.00
Low	High	60	55	0.93 (0.58–1.48)	1.02 (0.63–1.66)
High	Low	80	94	0.77 (0.51–1.16)	0.88 (0.58–1.36)
High	High	164	261	0.53 (0.36–0.78)	0.65 (0.43–0.97)
P trend				0.001	0.03

[a]Conditional logistic regression models with matched sets defined jointly by age (⩽39,40–44,45–49,50–54, 55–59, 60–64, 65–69, 70+) and Asian-ethnicity (Chinese, Japanese, Filipino) were employed. Birthplace, education, age at menarche, pregnancy, current BMI, menopausal status and use of menopausal hormones were included as covariates in all models.
[b]Further adjusted for intake of dark leafy greens during adolescence (<4 times/week, 4–6 times/week, daily), smoking history (no/yes), alcohol intake (no/yes), physical activity (0,1–19, 20+ years) and family history of breast cancer (no/yes).
[c]Monthly or less intake comprised low tofu intake during adolescence; weekly or more intake comprised high tofu intake during adolescence. Quartiles 1 and 2 defined low soy isoflavone intake during adult life; quartiles 3 and 4 represented high intake.

nativity. Intake of soy was highest among Chinese (26.8 mg/day), intermediate among Japanese (18.4 mg/day) and lowest among Filipino women (9.3 mg/day). In each Asian ethnic group, intake of soy was higher in migrants than in US-born women; intake level tended to slightly decrease with increasing years of residence in the US for the Chinese and Japanese but not for the Filipinos. Among Los Angeles County Asian-Americans, tofu eaten by itself or in mixed dishes was the main source of soy (based on isoflavones), accounting for some 60% of the soy foods eaten; soymilk (12%), miso (9%), fresh soy beans (5%), and other processed soy foods (5%) each accounted for a relatively small portion of the total soy intake (data not shown).

Table III shows the risk of breast cancer in association with intake of soy during adolescence and adult life. The ORs associated with adolescent tofu intake (less than once a month, one to three times per month, one to three times per week, four or more times per week, daily or more often) after adjustment for demographic and menstrual and reproductive factors were 1.00, 0.75, 0.56 and 0.51, respectively (*P* trend = 0.002). The adjusted ORs by quartile of isoflavone intake during adult life after adjustment for demographic and menstrual and reproductive factors were 1.00, 0.76, 0.69 and 0.51, respectively (*P* trend = 0.003). Table III also shows the results after adjustment for intake of dark leafy greens during adolescence, other adult lifestyle habits (e.g. physical activity, smoking, alcohol) and family history of breast cancer (adjusted OR[b], Table III). In this final model which considered all the potential confounders, the magnitude of the associations between risk and intake of soy during adolescence (*P* trend = 0.04) and intake during adult life weakened (*P* trend = 0.04).

We also classified subjects by their joint intake of soy during adolescence and adult life (Table III). The reduced risk of breast cancer was apparent among individuals who were high consumers during both time periods (OR=0.53, 95% CI= 0.36, 0.78). There was some suggestion of a reduction in risk among individuals who were high (i.e. at least weekly) consumers during adolescence but were low consumers (below median level of isoflavone intake) during adult life (OR=0.77, 95% CI=0.51–1.16). In contrast, there was no risk reduction among high (above median level of isoflavone intake) soy consumers during adult life who were low soy (i.e. monthly or less frequent) consumers during adolescence (OR=0.93, 95% CI=0.58–1.48). Results remained similar after adjustment

Table IV. Risk[a] of breast cancer in association with intake of soy during adolescence and adult life by Asian ethnicity, birthplace, menopausal status and intake of dark leafy greens during adolescence

[Cases/controls]	Intake of tofu during adolescence				Intake of isoflavones (mg/1000 kcal)-adult				
	Monthly or less	⩽1–3×/week	⩾4×/week	*P* trend	⩽1.79	>1.79–6.24	>6.24–12.68	>12.68	*P* trend
Asian ethnicity									
Chinese [160/228]	1.00	0.90	0.65	0.29	1.00	0.44	0.70	0.47	0.25
Japanese [146/175]	1.00	0.34[c]	0.37	0.14	1.00	1.24	0.93	0.57	0.07
Filipino [195/191]	1.00	0.57[c]	0.58	0.03	1.00	0.75	0.51[c]	0.46	0.02
Birthplace									
US born [126/163]	1.00	0.38[c]	0.57	0.22	1.00	0.81	0.71	0.41	0.06
Non-US born[b] [375/431]	1.00	0.70	0.54[c]	0.03	1.00	0.78	0.74	0.58[c]	0.05
Age									
<50 [209/307]	1.00	0.71	0.64	0.23	1.00	0.81	0.74	0.47[c]	0.04
50+ [292/287]	1.00	0.56[c]	0.45[c]	0.01	1.00	0.65	0.61	0.48[c]	0.02
Menopausal status									
Pre [208/289]	1.00	0.78	0.64	0.25	1.00	1.00	0.81	0.60	0.14
Post [283/304]	1.00	0.54[c]	0.41[c]	0.007	1.00	0.54[c]	0.57[c]	0.39[c]	0.005
Dark leafy green intake during adolescence									
⩽3×/week [219/184]	1.00	0.60	0.61	0.08	1.00	0.75	0.74	0.40[c]	0.04
4⩾/week [277/405]	1.00	0.64	0.60	0.13	1.00	0.81	0.70	0.60	0.08

[a]Conditional logistic regression models with matched sets defined jointly by age (⩽39,40–44,45–49,50–54, 55–59, 60–64, 65–69, 70+) and Asian-ethnicity (Chinese, Japanese, Filipino) were employed. Birthplace, education, age at menarche, pregnancy, current body mass index, menopausal status and use of menopausal hormones were included as covariates. In analyses that were stratified by specific variables, Asian-ethnicity (Chinese, Japanese, Filipino), birthplace, and menopausal status were excluded accordingly. In stratified analysis by age (<50 vs 50+), relevant age groups were included in the regression model for ages <50 and ages 50+ years.
[b]In the analysis among non-US born subject, years of residence in the US were also included.
[c]95% CI excluded 1.0.

for various potential confounders as described above (see adjusted OR[b], Table III).

The association between soy intake and breast cancer risk was examined separately by various subgroups including Asian ethnicity, nativity, age, menopausal status and high/low intake of dark leafy greens (Table IV). This pattern of risk reduction in association with soy intake during adolescence and adult life was observed in each of the Asian ethnic groups although the results were not statistically significant in some subgroups (Table IV). Similarly, a reduced risk of breast cancer in association with soy intake during both time periods of exposure was observed among US-born Asians and migrants. Results on soy were also in the same direction in younger (age <50 years) and older (age 50+ years) and in premenopausal and postmenopausal women. Results were statistically significant in both younger and older women and in postmenopausal women. As intake of dark leafy greens during adolescence may be a marker of intake of other components of the more traditional 'Asian diet', we evaluated the soy-breast cancer among high (four times or more per week) and lower (three times or less per week) consumers of dark leafy greens separately. An association between soy intake and risk was observed among both high and lower consumers of dark leafy greens.

In addition to isoflavones, other constituents in soy beans may have beneficial effects on risk of breast cancer. Risk reductions were observed in association with each type of soy foods; significant risk reductions were observed for the main sources of soy in this population which included tofu, eaten by itself or in mixed dishes, fresh soy beans and fried tofu (*P* trend < 0.05 for each of these foods). Reduction in risk was also found in association with high intake of miso (*P* trend = 0.09) and intake of soy milk (*P* trend = 0.10).

Discussion

This case-control study has been designed specifically to investigate the role of traditional Asian whole soy foods in association with breast cancer development among Asian-American women in Los Angeles County. Our results suggest that soy food intake during adolescence and adult life is associated with a significant reduced risk of breast cancer. Although the results on soy and risk did not reach statistical significance in some subgroup analyses, this pattern of risk reduction was consistently observed in each of the three Asian ethnic groups studied, in US-born women and migrants, in younger and older women, in premenopausal and postmenopausal women and among high and lower consumers of dark leafy greens. Our finding in relation to the timing of soy exposure is particularly intriguing. Similar to the results reported by Shu *et al*. (9) from Shanghai, soy intake during adolescence had a significant effect on risk that was more pronounced than the effect of adult soy intake. In addition, there is a suggestion of lasting protection associated with high soy consumption during adolescence. Subjects who were low-soy consumers during adult life but were high-soy consumers during adolescence showed a 23% reduction in risk, although this was not statistically significant. In contrast, in the small group of subjects who were low-soy consumers during adolescence and high-soy consumers in adult life (60 cases and 55 controls), there was little difference in their risk compared with women who were low-soy consumers during both time periods. Studies with larger sample sizes will be needed to confirm this result. If true, it has important implications in terms of prevention strategies using soy or other similar agents.

There is support from animal studies that early life exposure to genistein, the main isoflavone in soy beans, may be associated with a significant reduction in the number of

chemically induced mammary tumors. Pharmacological (genistein at 500 mg/kg body wt) (15) or physiological doses of genistein (1 mg/kg body wt) were injected (16) or physiological amounts (25 and 250 mg genistein/kg diet) were added in the diet (17) in these experiments. These investigators found that genistein exposure favorably influenced mammary gland morphology, resulting in a reduction in the number of terminal end buds and increasing the ratio of lobules to terminal end buds (ratio of most differentiated to least differentiated terminal ductal structures) (16,17). These observations led to the hypothesis that early life exposure to genistein may have a lasting benefit in terms of breast cancer risk by enhancing mammary gland differentiation (18–20).

Other mechanisms that have been implicated focus on the potential effects of soy on hormone production and metabolism (19–21). Although not all consistent, there is accumulating evidence from short-term dietary intervention studies and cross-sectional studies that high soy intake may be associated with reduced endogenous estrogen levels (see below). There are also supportive data from *in vitro* studies that genistein has inhibitory effects on several key enzymes involved in estrogen metabolism including aromatase, 17β-hydroxysteroid dehydrogenase and 3β-hydroxysteroid dehydrogenase (19,21). Soy's effect on breast cancer development may be intimately related to genistein's preferential binding to estrogen receptor β (ERβ) and its potent repression of ERβ-mediated genes while having less effect on estrogen receptor α (ERα)-mediated genes (22,23).

If the beneficial effects of Asian soy foods on breast health suggested in this and other studies can be accepted at face value, how much soy food is needed? Until recently, little data were available to evaluate the amount of soy foods needed to have an effect on breast health as the assessment of soy intake was relatively crude in most of the studies published in the 1990s (24). A picture is now emerging regarding dose–response relationships between adult soy intake and breast cancer risk. Intake of soy among the Asian-American women in Los Angeles County (median daily intake of isoflavones was 12 mg) appears comparable with that consumed by Chinese women in Singapore (25). However, intake in our study was considerably lower than that in Shanghai (median daily intake was 33 mg of isoflavones) (10). The much lower soy intake among non-Asians in the San Francisco Bay Area (11) may explain, in part, the null association reported in this large study. In Shanghai, a reduction in risk was observed between those in the lowest decile of soy intake (2.7 gm soy protein/day or ~10 mg isoflavones/day) and those not in the lowest decile of intake. However, there was not a smooth trend of decreasing risk with increasing amounts consumed (10). A plateau level may exist so that there may be little additional benefit above a certain level of soy intake. It is of interest that in Los Angeles County, the median soy intake (12 mg isoflavones) is close to the lowest decile intake in the Shanghai study (10 mg isoflavones). In our study, a risk reduction was most apparent among individuals in the highest quartile of intake (see Table III, adjusted OR[b]).

Our study represents one of three population-based, case-control epidemiologic studies that has been designed specifically to investigate further the role of soy in breast cancer risk (10,11). The sample size of our study provided a power of at least 80% to detect an OR of 0.6 between the upper and lower quartile of soy intake. However, a larger sample size is needed to sort out definitively the effects of timing of soy exposure and whether certain dietary or non-dietary risk factors modify the soy-breast cancer association. Our study has the advantage of including three Asian ethnic groups who are soy consumers, but whose intakes differ considerably (daily mean intake of isoflavones ranged from 9 mg among Filipinos to 27 mg among Chinese) and providing a wide range for study. In addition to the supportive evidence from some epidemiologic studies (1–3,7–10), high intake of soy has been associated with lower endogenous estrogen levels in cross-sectional studies conducted in Asia (25,26) and in some short-term soy intervention studies (see reviews in refs 19,21). Provocative protective effects of soy on mammographic density have been reported in a cross-sectional study of some 400 Chinese women in Singapore (27). In this study, Jakes *et al.* (27) correlated mammographic density with information on soy intake that was obtained as part of a baseline assessment for a cohort study in Singapore. Detailed information on various lifestyle and dietary habits (including soy intake) was collected some 1.8 years prior to the mammographic examination. These investigators found that dietary soy protein intake was significantly inversely related to risk of mammographic density patterns, providing corroborative evidence that high soy intake may reduce breast cancer risk.

Notwithstanding, there are several limitations with this case-control study. We were able to interview only 60% of the reported cases. The largest loss was due to refusal by the cases (23%) or their physicians (5%) or the subjects (11%) had moved outside of Los Angeles County. This modest interview rate raises several methodological issues, the most important of which is the comparability of interviewed and non-interviewed cases in terms of intake of soy, the primary exposure of interest. Place of birth was available on some 60% of the subjects we failed to interview; 15% of these women were born in the US. Among the cases we interviewed, 25% of them were US born. As intake of soy is lower among US-born subjects and assuming that the pattern of soy intake is similar between those we interviewed and failed to interview, our estimate of risk associated with soy intake may be an underestimate of the true association.

A second limitation that applies to this and other studies on soy and breast cancer is the extent to which soy intake is a marker of some other lifestyle factor or factors that are causally related to breast cancer risk. We have attempted to address this issue by carefully adjusting for potential confounders and conducting subgroup analyses that may reveal such differences. Adult intake of plant foods rich in fiber and various micronutrients (e.g. carotenoids, vitamin C, folate) were not potential confounders for the soy-breast cancer association in this population. Although our assessment of dietary patterns during adolescence was very crude, we have used intake of dark leafy greens during adolescence as a surrogate marker of other aspects of early life diet that might be important in breast cancer risk. Interestingly, in more homogeneous eastern (9) and western populations (28), few strong influences of dietary intakes during adolescence on risk of breast cancer have emerged.

In conclusion, results from this study of breast cancer in Asian-Americans suggest that soy food intake, particularly during early life, may have a lasting protective effect on breast cancer risk. A much larger study is needed to sort out the added benefits of adult soy intake and the levels of intake

needed. Data on early life and adult intake of soy from prospective cohort studies will be needed to confirm these results from case-control studies.

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References

1. Lee,H.P., Gourley,L., Duffy,S.W., Esteve,J., Lee,J. and Day,N.E. (1991) Dietary effects on breast cancer risk in Singapore. *Lancet*, **331**, 1197–1200.
2. Lee,H.P., Gourley,L., Duffy,S.W., Esteve,J., Lee,J. and Day,N.E. (1992) Risk factors for breast cancer by age and menopausal status: a case-control study in Singapore. *Cancer Causes Control*, **3**, 313–322.
3. Hirayama,T. (1990) Life-style and mortality. A large-scale census-based cohort study in Japan. In Wahrendorf,J. (ed) *Contributions to Epidemiology and Biostatistics*. Karger, Basel, Vol. 6.
4. Key,T.J., Sharp,G.B., Appleby,P.N., Beral,V., Goodman,M.T., Soda,M. and Mabuchi,K. (1999) Soya foods and breast cancer risk: A prospective study in Hiroshima and Nagasaki, Japan. *Br. J. Cancer*, **81**, 1238–1256.
5. Hirose,K., Tajima,K., Hamajima,N., Inoue,M., Takezaki,T., Kuroishi,T., Yoshida,M. and Tokudome,S. (1995) A large-scale, hospital-based case-control study of risk factors of breast cancer according to menopausal status. *Jpn J. Cancer Res.*, **86**, 146–154.
6. Yuan,J.M., Wang,Q.S., Ross,R.K., Henderson,B.E. and Yu,M.C. (1995) Diet and breast cancer in Shanghai and Tianjin, China. *Br J. Cancer*, **71**, 1353–1358.
7. Wu,A.H., Ziegler,R.C., Horn-Ross,P.L., Nomura,A.M.Y., West,D.W., Kolonel,L.N., Rosenthal,J.R., Hoover,R.N. and Pike,M.C. (1996) Tofu and risk of breast cancer in Asian-Americans. *Cancer Epidemiol. Biomarkers Prev.*, **5**, 901–906.
8. Witte,J.S., Ursin,G., Siemiatycki,J., Thompson,W.D., Paganini-Hill,A. and Haile,R.W. (1997) Diet and premenopausal bilateral breast cancer: a case-control study. *Breast Cancer Res. Treat.*, **42**, 243–251.
9. Shu,X.O., Jin,F., Dai,Q., Wen,W., Potter,J.D., Kushi,L.H., Ruan,Z., Gao,Y.-T. and Zheng,W. (2001) Soyfood intake during adolescence and subsequent risk of breast cancer among Chinese women. *Cancer Epidemiol. Biomarkers Prev.*, **10**, 483–488.
10. Dai,Q., Shu, X-O., Jin,F., Potter,J.D., Kushi,L.H., Teas,J., Gao,Y.-T. and Zheng,W. Population-based case-control study of soyfood intake and breast cancer risk in Shanghai. *Br. J. Cancer*, **85**, 372–378.
11. Horn-Ross,P.L., John,E.M., Lee,M., Stewart S.L., Koo,J., Sakoda,L.C., Shiau,A.C., Goldstein,J., Davis,P. and Perez-Stable,E.J. (2001) Phytoestrogen consumption and breast cancer risk in a multiethnic population. *Am. J. Epidemiol.*, **154**, 434–441.
12. Kolonel,L.N., Henderson,B.E., Hankin,J.H., Nomura,A.M.Y., Wilkens,L.R., Pike M.C., Stram,D.O., Monroe,K.R., Earle,M.E. and Nagamine,F.S. (2000) A multiethnic cohort in Hawaii and Los Angeles: Baseline characteristics. *Am. J. Epidemiol.*, **151**, 346–357.
13. Stram,D.O., Hankin,J.H., Wilkens,L.R., Pike,M.C., Monroe,K.R., Park,S., Henderson,B.E., Nomura,A.M.Y., Earle,M.E., Nagamine,F.S. and Kolonel,L.N. (2000) Calibration of the dietary questionnaire for a multiethnic cohort in Hawaii and Los Angeles. *Am. J. Epidemiol.*, **151**, 358–70.
14. Breslow,N.E. and Day,N.E. (1980) *Statistical Methods in Cancer Research. Vol 1. The Analysis of Case-Control Studies*. IARC Scientific Publications No. 32. Lyon.
15. Murrill,W.B., Brown,N.M., Zhang,J.X., Manzolillo,P.A., Barnes,S. and Lamartiniere,C.A. (1996) Prepubertal genistein exposure suppresses mammary cancer and enhances gland differentiation in rats. *Carcinogenesis*, **17**, 1451–1457.
16. Hilakivi-Clarke,L., Onojafe,I., Raygada,M., Cho,E., Skaar,T., Russo,I. and Clarke,R. (1999) Prepubertal exposure to zearalenone or genistein reduces mammary tumorigenesis. *Br. J. Cancer*, **80**, 1682–1688.
17. Fritz W.A., Coward,L., Wang,J., Lamartiniere,C.A. (1998) Dietary genistein: perinatal mammary cancer prevention, bioavailability and toxicity testing in the rat. *Carcinogenesis*, **19**, 2151–2158.
18. Lamartiniere,C.A. (2000) Protection against breast cancer with genistein: a component of soy. *Am. J. Clin. Nutr.*, **71**, 1705s–1707s.
19. Messina,M.J. and Loprinzi,C.L. (2001) Soy for breast cancer survivors: a critical review of the literature. *J. Nutr.*, 131, 3095S–3108S.
20. Bouker,K.B. and Hilakivi-Clarke,L. (2000) Genistein: does it prevent or promote breast cancer? *Environ. Health Perspect.*, **108**, 701–708.
21. Kurzer,M.S. (2000) Hormonal effects of soy isoflavones: studies in premenopausal and postmenopausal women. *J. Nutr.*, 130, 660s–661s.
22. Kuiper,G.G., Carlsson,B., Grandien,K., Enmark,E., Haggblad,J., Nilsson,S. and Gustafsson,J.A. (1997) Comparison of the ligand binding specificity and transcript tissue distribution of estrogen receptors alpha and beta. *Endocrinology*, **138**, 863–870.
23. An,J., Tzagarakis-Foster,C., Scharschmidt,T.C., Lomri,N. and Leitman,D.C. (2001) Estrogen receptor β-selective transcriptional activity and recruitment of coregulators by phytoestrognes. *J. Biol. Chem.*, **276**, 17808–17814.
24. Wu,A.H. and Pike,M.C. (2002) Phytoestrogen content in foods and their role in cancer. In Cadenas,E. and Packer,L. (eds) *Handbook of Antioxidants*. Marcel Dekker, Inc., New York, pp. 337–350.
25. Wu,A.H., Stanczyk,F.Z., Seow,A., Lee,H.P., Yu,M.C. (2002) Soy intake and other lifestyle determinants of serum estrogen levels among postmenopausal Chinese women in Singapore. *Cancer Epidemiol. Biomarkers Prev.*, in press
26. Nagata,C., Kabuto,M., Kurisu,Y. and Shimizu,H (1997) Decreased serum estradiol concentration associated with high dietary intake of soy products in premenopausal Japanese women. *Nutr. Cancer*, **29**, 228–233.
27. Jakes,R.W., Duffy,S.W., Ng,F.C., Gao,F., Ng,E.H., Seow,A., Lee,H.P. and Yu,M.C. (2002) Mammographic parenchymal patterns and self-reported soy intake in Singapore Chinese women. *Cancer Epidemiol. Biomarkers Prev.*, **11**, 608–613.
28. Potischman,N., Weiss,H.A., Swanson,C.A., Coates,R.J., Gammon,M.D., Malone,K.E., Brogan,D., Stanford,J.L., Hoover,R.N., Brinton,L.A. (1998) Diet during adolescence and risk of breast cancer among young women. *J. Natl Cancer Inst.*, **90**, 226–233.

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