

Childhood Soy Intake and Breast Cancer Risk in Asian American Women

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Abstract

Introduction: Historically, breast cancer incidence has been substantially higher in the United States than in Asia. When Asian women migrate to the United States, their breast cancer risk increases over several generations and approaches that for U.S. Whites. Thus, modifiable factors, such as diet, may be responsible.

Methods: In this population-based case-control study of breast cancer among women of Chinese, Japanese, and Filipino descent, ages 20 to 55 years, and living in San Francisco-Oakland (California), Los Angeles (California) and Oahu (Hawaii), we interviewed 597 cases (70% of those eligible) and 966 controls (75% about adolescent and adult diet and cultural practices. For subjects with mothers living in the United States (39% of participants), we interviewed mothers of 99 cases (43% of eligible) and 156 controls (40%) about the daughter's childhood exposures. Seventy-three percent of study participants were premenopausal at diagnosis.

Results: Comparing highest with lowest tertiles, the multivariate relative risks (95% confidence interval) for childhood, adolescent, and adult soy intake were 0.40 (0.18-0.83; $P_{\text{trend}} = 0.03$), 0.80 (0.59-1.08; $P_{\text{trend}} = 0.12$), and 0.76 (0.56-1.02; $P_{\text{trend}} = 0.04$), respectively. Inverse associations with childhood intake were noted in all three races, all three study sites, and women born in Asia and the United States. Adjustment for measures of westernization attenuated the associations with adolescent and adult soy intake but did not affect the inverse relationship with childhood soy intake.

Discussion: Soy intake during childhood, adolescence, and adult life was associated with decreased breast cancer risk, with the strongest, most consistent effect for childhood intake. Soy may be a hormonally related, early-life exposure that influences breast cancer incidence. (Cancer Epidemiol Biomarkers Prev 2009;18(4):1050-9)

Introduction

Breast cancer rates are consistently higher in Western countries than in Asia (1); yet, among Asian migrants to the United States, breast cancer risk increases over several generations and eventually approaches that for U.S. White women (2). Thus, the protective factors, presumably related to Asian diet and lifestyle, are modifiable and not genetic. Early studies suggested that the increase in breast cancer risk did not appear until the second generation, among Asians born in the United States, contrary to the patterns noted for other major cancers (3). Therefore, it was hypothesized that exposure to Western lifestyle at an early age was critical in breast carcinogenesis (3-5). These intriguing observations were the rationale for our study of breast cancer in Asian American women, in which we sought to elucidate the lifestyle and environmental factors responsible for increased risk in the West.

Epidemiologic studies of adult soy intake and breast cancer risk have reported mixed results (6), although studies in Asian and Asian American populations have generally suggested that soy is protective, possibly

because of higher levels of soy consumption (7-13). A recent meta-analysis of soy intake and breast cancer concluded that strong support exists for the hypothesis that soy intake in the amount consumed in Asian populations is protective against breast cancer (14). More consistent, and perhaps more intriguing, are three studies examining adolescent intake, each of which showed a decreased risk of breast cancer among women with high soy (15, 16) or phytoestrogen (17) intake. Early-life exposures are increasingly being recognized as important in breast carcinogenesis (18) and may act by altering the hormonal milieu (19). It is plausible that soy intake early in life affects breast cancer risk through a hormonal mechanism, as numerous animal studies and some clinical data have suggested that soy has weak estrogenic properties (20, 21). Furthermore, several investigators have proposed that age at consumption of phytoestrogens influences their effect on breast cancer risk (6, 22-24). To our knowledge, our study is the first to address the association between childhood soy intake and breast cancer risk.

We have previously described a modest inverse association between adult tofu intake and breast cancer risk in this population-based case-control study in Asian American women (12). In the present analysis, we use the wide variation in soy intake in this migrant population to examine the effects of soy intake across the lifespan. We seek to characterize the relative contributions of soy

Received 5/3/08; revised 11/12/08; accepted 1/28/09; published OnlineFirst 3/24/09.

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doi:10.1158/1055-9965.EPI-08-0405

intake during childhood, adolescence, and adulthood and to evaluate whether soy is itself protective or merely an indicator of other Asian lifestyles that reduce breast cancer risk.

Materials and Methods

Study Design and Subjects. The design of our population-based case-control study of breast cancer in Asian American women has been described in detail previously (2, 25-27). Briefly, eligible cases were all women of Chinese, Japanese, or Filipino descent diagnosed with histologically confirmed, first primary breast cancer at ages 20 to 55 years in the Los Angeles County Metropolitan Statistical Area, the San Francisco-Oakland Metropolitan Statistical Area, or Oahu, Hawaii between April 1, 1983 and June 30, 1987. Older women were excluded because we wished to interview the mothers of the subjects, to the extent possible, about the childhood exposures of the subjects.

Potential controls at the two California study sites were selected by random-digit dialing and frequency matched to the expected case distribution on study site, ethnicity, and year of birth (in 5-year groups) using a ratio of 2:1 whenever possible. The households selected by random-digit dialing as potential sources of controls were first screened to determine the ethnicity and age range of all females receiving phone calls at that number. A total of 18,680 households were contacted in Los Angeles and 15,265 households in San Francisco-Oakland. The response rate for the screening interview, after successive calls if necessary, was 92% in Los Angeles and 91% in San Francisco-Oakland. Nonresponding households either could not be contacted after successive attempts or refused to complete the household census. All women who received phone calls at a selected phone number and were of the correct age and ethnicity were considered eligible for the study, and controls were randomly selected from the pool of eligible women. Potential controls from Oahu were selected through the Hawaii Health Surveillance Program, which annually samples households in the State, and were individually matched to eligible cases on age (in 5-year groups) and ethnicity in a 2:1 ratio whenever possible.

To be eligible for the study, cases and controls had to be at least 50% Chinese, Japanese, or Filipino or at least 50% a mixture of these ethnicities. Approximately 94% of cases and 96% of controls considered themselves to be of a single ethnicity (Chinese, Japanese, or Filipino).

Of 852 eligible cases, 597 (70%) participated; of 1,287 eligible controls, 966 (75%) participated. Participation rates were similar for the three races and three study sites (2).

To collect additional information about childhood exposures, we attempted to interview participants' mothers who were alive and living in the United States. For the cases and controls, respectively, 43% and 36% of the mothers had died and 19% and 25% lived outside of the United States. Therefore, the mothers of 233 cases and 379 controls (39% of all participants) were eligible for interview. Of the eligible mothers, 99 mothers of cases (43% of those eligible) and 156 mothers of controls (40% of those eligible) were successfully interviewed. The major reasons for nonparticipation were the daughter not

consenting for her mother to be contacted (33% of cases and 38% of controls), maternal language problems (10% of cases and 7% of controls), and the mother refusing to participate (6% of cases and 6% of controls).

Exposure Assessment. Cases and controls were interviewed in their homes by trained staff using structured questionnaires. Mothers were interviewed by telephone, also with structured questionnaires. Each interview was conducted in the language chosen by the person being interviewed.

The subject interview elicited information on race, residential history, birthplace of parents and grandparents, medical and family history, menstrual and reproductive history, anthropometry, diet during adolescent and adult life, and cultural and religious practices during adolescent and adult life. Usual dietary patterns during adolescent and adult life were each assessed using 65-item, ethnicity-specific food frequency questionnaires as described previously (12). Frequency of intake was recorded in times per day, week, month, or year, whichever timeframe was most convenient for the food item and respondent. Usual portion size was not assessed. Adolescence was defined as ages 12 to 19 years; adult life was defined as beginning at age 20 years and excluding the most recent 3 years. If changes in diet had occurred during either interval, usual intake was asked for the longest period of stable diet. For adult diet, 90% of subjects reported a stable dietary pattern for ≥ 10 years. The mean number of years of a stable diet during adulthood was 19 years. For adolescent diet, 91% reported a stable diet for at least 4 years of the 7-year period. The mean number of years of a stable diet during adolescence was 6.6 years.

The interview for mothers was similar and used the same food frequency and cultural and religious practices questions as the subject interview. Mothers were asked about their daughter's diet and family lifestyle during her childhood (ages 5-11 years). If childhood diet had changed, usual intake was asked for the longest period of stable diet. More than 95% of mothers reported that their daughter had a stable diet during these 7 years.

For Chinese American and Filipino American participants, soy intake was based on the usual frequency of intake of "a tofu dish made with any fresh, dried, or deep-fried tofu product." For Japanese American participants, soy intake was based on a weighted sum of usual frequencies of intake of tofu, miso (soybean paste) soup, and natto (fermented soy bean; ref. 12). Food frequency interviews without answers to $\geq 20\%$ of the questions were excluded from analysis, including 5 reports for childhood diet, 45 reports for adolescent diet, and 10 reports for adult diet. Values for missing food frequencies were imputed by two methods. If a respondent indicated that she (or her daughter) ate a certain food, but she did not know how often, the median of nonzero responses for that food was imputed (on average, 1% of subjects for adult and adolescent diet and 4% of mothers for childhood diet). If a respondent did not know whether a certain food was consumed, the median of all responses, including zero responses, for that food was imputed (on average, 0.5% of subjects for adult and adolescent diet and 1% of mothers for childhood diet). The medians for imputation were calculated separately for childhood, adolescent, and adult diet and for each ethnicity.

Statistical Methods. All statistical analyses were done using SAS (version 9.13). We used χ^2 tests to compare the distributions for matching variables and accepted breast cancer risk factors in cases and controls and in mothers who were and were not interviewed. Correlations between soy intake during childhood, adolescence, and adulthood were expressed as Spearman correlation coefficients for continuous forms of the variables.

Relative risks (RR) for breast cancer, as estimated by odds ratios, and 95% confidence intervals (95% CI) were calculated using unconditional logistic regression. Key results were also analyzed using conditional regression, which produced similar results. Soy intake was stratified as tertiles, based on the frequency distribution of intake among controls in each period, and the lowest tertile of intake was used as the reference category. *P* values for trend were calculated by assigning to each tertile the median value of soy intake for all subjects in the tertile.

For each period, confounding of the soy-breast cancer association was assessed by adding singly each potential breast cancer risk factor (age at menarche, age at first live birth, parity, menopausal status at diagnosis, personal history of benign breast disease, first- or second-degree family history of breast cancer) to a logistic regression model containing the matching variables used in the study design [race (Chinese, Japanese, Filipino), study area (Los Angeles Metropolitan Statistical Area; San Francisco-Oakland Metropolitan Statistical Area; Oahu, HI), and age at diagnosis (20-39, 40-44, 45-49, ≥ 50 years)]. Age at diagnosis was collapsed into four strata because this simplification of the model gave substantively the same results as including age at diagnosis stratified into 5-year age groups. Any variable that altered the risk estimate by $\geq 10\%$ for childhood, adolescent, or adult soy intake was considered a confounder and included in the models for all three periods. Only age at first live birth and parity were confounders by this criterion. Two multivariate models for the associations between soy intake and breast cancer are presented. The simplified model includes study design matching variables and a variable combining parity and age at first live birth. The fully adjusted model, presented unless otherwise specified, also includes age at menarche, menopausal status at diagnosis, family history of breast cancer, and personal history of benign breast disease.

We examined effect modification of the soy-breast cancer association for each of the three periods using stratified analyses and logistic regression models which included interaction terms for soy intake and the variable of interest.

For analysis of Western versus Asian lifestyle, multiple measures of acculturation were used. To mirror the analysis of soy intake, cultural and lifestyle variables were derived from the mother's interview for the childhood period and from the subject's interview for the adolescent and adult periods. For each regression model, the most "Western" practice (Western religion and English language) was used as the reference category. We adjusted soy intake during each period for individual cultural and lifestyle variables and, in addition, for migration history, which was shown previously to be a strong predictor of breast cancer risk in this migrant population and integrated various determinants of acculturation (2). Migration history was

characterized by a composite variable that included birthplace of subject, birthplace of all four grandparents, and the total number of years lived in the West.

Results

Participant characteristics are presented in Table 1. Among all participants, as well as those whose mothers were interviewed, cases were more likely to be nulliparous or older (ages ≥ 21 years) at the birth of their first child, less likely to have multiple births, and more likely to report a family history of breast cancer and a personal history of benign breast disease. Only mothers who were alive and living in the United States were eligible for interview. Therefore, the subset of women whose mothers were interviewed, when compared with the women whose mothers were not interviewed, were younger at diagnosis (median age, 40 and 46 ages, respectively) and more likely to be premenopausal (88% versus 69%; Table 1). The women whose mothers were interviewed were also more likely to be Japanese and less likely to be Filipino. They were younger at menarche (mean, 12.3 versus 13.2 years), had fewer live births (mean, 1.7 versus 2.2), and were more likely to have a personal history of benign breast disease. After adjustment for age and place of birth of the study subject, which influenced whether we attempted to contact the mother, only age at menarche and history of benign breast disease remained significantly different.

Frequency of soy intake during adolescence and adulthood, both reported by the subject, were moderately correlated ($r = 0.64$). The correlation was somewhat weaker ($r = 0.43$) for childhood intake (reported by mother) and adolescent intake and substantially weaker ($r = 0.28$) for childhood and adult intake. The estimated frequency of soy intake was highest during adolescence (among controls, mean, 1.7 times a week), intermediate during childhood (mean, 1.3 times a week), and lowest during adulthood (mean, 1.2 times a week). Soy intake was lower in the subset of women for whom mothers were interviewed (mean adult soy intake, 0.8 times a week; mean adolescent soy intake, 1.1 times a week) but still greater than that reported in the literature for non-Asian women living in California (28).

Increasing soy intake during childhood, adolescence, and adulthood were each associated with decreased risk of breast cancer (Table 2). The inverse relationship was strongest for childhood soy intake (RR for highest tertile relative to lowest, 0.40; 95% CI, 0.18-0.83; $P_{\text{trend}} = 0.03$) but approached statistical significance for adolescent soy intake (RR, 0.80; 95% CI, 0.59-1.08; $P_{\text{trend}} = 0.12$) and reached statistical significance for adult soy intake (RR, 0.76; 95% CI, 0.56-1.02; $P_{\text{trend}} = 0.04$). For each of the three periods, comparing extremes of soy intake by stratifying intake into quartiles or hexiles did not strengthen the association (data not shown).

Analyses using the same absolute cut points to categorize soy intake in all three periods (low, 0 to <1 times a week; medium, 1 to <1.5 times a week; and high, ≥ 1.5 times a week) yielded similar results to those based on period-specific tertiles. The fully adjusted RR (95% CI) for high versus low soy intake were 0.47 (0.22-0.98) for childhood soy intake, 0.80 (0.61-1.06) for adolescent intake, and 0.76 (0.57-1.01) for adult intake. Limiting

analyses to those subjects who reported a stable diet for the entirety of each period also produced similar results (data not shown). Restricting the analyses for adolescent and adult soy intake to the subset of women for whom mothers were interviewed and childhood soy intake was evaluated minimally changed the risk for adolescent intake (RR, 0.74; 95% CI, 0.34-1.59) and attenuated the point estimate for adult intake (RR, 0.93; 95% CI, 0.45-1.93). Additional adjustment for body mass index did not alter the point estimates for any period (for childhood soy: RR, 0.40; 95% CI, 0.19-0.86; for adolescent soy: RR,

0.78; 95% CI, 0.57-1.06; and for adult soy: RR, 0.76; 95% CI, 0.56-1.03).

For childhood soy intake, breast cancer risk decreased with increasing intake in all three ethnic groups and all three study centers. Results were not as consistent for adolescent and adult soy intake. For both, inverse associations were seen for only two races (Japanese and Filipino for adolescent soy intake and Chinese and Filipino for adult soy intake) and two study centers (Los Angeles and San Francisco for both adolescent and adult soy intake). For adolescent and adult soy intake,

Table 1. Characteristics of study participants: comparison of cases and controls for all study participants and for subset whose mothers were interviewed and comparison of study participants by whether mother was interviewed

	All study participants		Subset with data from mothers		All study participants	
	No. (%) cases (n = 597)	No. (%) controls (n = 966)	No. (%) cases (n = 99)	No. (%) controls (n = 156)	No. (%) mothers interviewed (n = 255)	No. (%) mothers not interviewed (n = 1,308)
Age at diagnosis*						
20-39	137 (23)	270 (28)	35 (36)	75 (48)	110 (43)	297 (23)
40-44	108 (18)	191 (20)	32 (32)	36 (23)	68 (27)	231 (18)
45-49	154 (26)	190 (20)	19 (19)	29 (19)	48 (19)	296 (23)
≥50	198 (33)	315 (33)	13 (13)	16 (10)	29 (11)	484 (37)
	P = 0.05		P = 0.15		P < 0.0001	
Race						
Chinese	164 (27)	288 (30)	26 (26)	51 (33)	77 (30)	375 (29)
Japanese	239 (40)	395 (41)	53 (54)	82 (52)	135 (53)	499 (38)
Filipino	194 (33)	283 (29)	20 (20)	23 (15)	43 (17)	434 (33)
	P = 0.17		P = 0.17		P = 0.0007	
Study center						
Hawaii	213 (36)	379 (39)	38 (39)	84 (54)	122 (48)	470 (36)
Los Angeles	215 (36)	274 (28)	28 (28)	23 (15)	51 (20)	438 (34)
San Francisco-Oakland	169 (28)	313 (32)	33 (33)	49 (31)	82 (32)	400 (31)
	P = 0.90		P = 0.12		P = 0.07	
Parity						
Nulliparous	145 (25)	148 (15)	38 (38)	24 (15)	62 (24)	231 (18)
1 live birth	85 (14)	141 (15)	19 (19)	34 (22)	53 (21)	173 (13)
2-3 live births	288 (49)	481 (50)	37 (38)	76 (49)	113 (44)	656 (51)
≥4 live births	73 (12)	188 (20)	5 (5)	22 (14)	27 (11)	234 (18)
	P < 0.0001		P < 0.0001		P = 0.31 [†]	
Age at first live birth						
Nulliparous	145 (25)	148 (15)	38 (38)	24 (15)	62 (24)	231 (18)
≤20	30 (5)	96 (10)	2 (2)	18 (12)	20 (8)	106 (8)
21-30	314 (53)	583 (61)	39 (40)	92 (59)	131 (51)	766 (59)
≥31	101 (17)	128 (13)	20 (20)	22 (14)	42 (17)	187 (15)
	P = 0.06		P = 0.02		P = 0.67 [†]	
Menopausal status at diagnosis						
Premenopausal	438 (74)	684 (71)	88 (89)	136 (87)	224 (88)	898 (69)
Postmenopausal	151 (26)	277 (29)	11 (11)	20 (13)	31 (12)	397 (31)
	P = 0.17		P = 0.68		P = 0.92 [†]	
Age at menarche						
≤11	105 (18)	160 (17)	19 (19)	48 (31)	67 (26)	198 (15)
12-13	284 (48)	457 (48)	60 (61)	82 (53)	142 (56)	599 (46)
14-15	138 (23)	225 (23)	16 (16)	21 (13)	37 (15)	326 (25)
≥16	63 (11)	117 (12)	4 (4)	4 (3)	8 (3)	172 (13)
	P = 0.36		P = 0.07		P = 0.004 [†]	
Family history of breast cancer						
First- or second-degree relative	117 (20)	92 (10)	18 (18)	22 (14)	40 (16)	169 (13)
No relatives	480 (80)	874 (90)	81 (82)	134 (86)	215 (84)	1139 (87)
	P < 0.0001		P = 0.38		P = 0.67 [†]	
Personal history of benign breast disease						
Yes	104 (18)	98 (10)	23 (23)	22 (14)	45 (18)	162 (13)
No	469 (82)	840 (90)	76 (77)	134 (86)	210 (82)	1134 (87)
	P < 0.0001		P = 0.06		P = 0.05 [†]	

*An age comparable with the age at diagnosis of breast cancer was assigned to each of the controls based on the ages at diagnosis of the frequency-matched cases (2).

[†]P values are adjusted for subject's age and place of birth, as these variables reflect the basis for identifying the mothers eligible for interview.

Table 2. RR of breast cancer and 95% CI by tertiles of soy intake during childhood, adolescence, and adulthood

Soy intake*	Range (times/wk)	Cases/controls	RR (95% CI) [†] simplified model	RR (95% CI) [‡] fully adjusted model
Childhood (mother interviewed)				
Low	0-0.75	41/50	1.0	1.0
Medium	0.76-1.49	30/51	0.44 (0.21-0.93)	0.43 (0.20-0.96)
High	1.50-8.8	26/52	0.42 (0.20-0.90)	0.40 (0.18-0.86)
<i>P</i> for highest vs lowest tertile of intake			0.02	0.07
<i>P</i> _{trend} [§]			0.02	0.03
Adolescence (subject interviewed)				
Low	0-0.50	215/315	1.0	1.0
Medium	0.51-1.9	186/303	0.92 (0.69-1.22)	0.95 (0.71-1.27)
High	2.0-8.9	175/324	0.77 (0.57-1.04)	0.80 (0.59-1.08)
<i>P</i> for highest vs lowest tertile of intake			0.09	0.15
<i>P</i> _{trend} [§]			0.08	0.12
Adulthood (subject interviewed)				
Low	0-0.43	205/298	1.0	1.0
Medium	0.44-1.10	222/339	1.00 (0.77-1.30)	0.99 (0.76-1.30)
High	1.11-12.0	164/325	0.71 (0.53-0.95)	0.76 (0.56-1.02)
<i>P</i> for highest vs lowest tertile of intake			0.03	0.02
<i>P</i> _{trend} [§]			0.01	0.04

*Soy intake was stratified as tertiles based on the frequency distribution of intake among controls in each period, and the low tertile was used as the reference category.

[†]The simplified model is adjusted for study design variables [age at diagnosis (20-39, 40-44, 45-49, ≥50 y), ethnicity (Chinese, Japanese, Filipino), and study center (Hawaii, Los Angeles, San Francisco-Oakland)] and parity/age at first live birth (nulliparous/never pregnant, 1-2 live births/age at first birth ≤20 y, ≥3 live births/age at first live birth ≤20 y, 1-2 live births/age at first live birth ≥21 y, ≥3 live births/age at first live birth ≥21 y, missing).

[‡]The fully adjusted model includes study design variables and known breast cancer risk factors: parity/age at first live birth (stratified into six categories as described above), menopausal status at diagnosis (premenopausal, postmenopausal, missing/other), age at menarche (<13 y, ≥13 y, missing/other), family history of breast cancer (yes, no), and personal history of benign breast disease (yes, no, missing).

[§]*P* values for trend were calculated by assigning to each tertile the median soy intake for all subjects in the tertile.

comparable inverse associations were noted for premenopausal and postmenopausal breast cancer (for highest versus lowest tertile of adolescent soy intake: odds ratio, 0.79; 95% CI, 0.56-1.12 for premenopausal breast cancer and odds ratio, 0.71; 95% CI, 0.37-1.33 for postmenopausal breast cancer; for highest versus lowest tertile of adult soy intake: odds ratio, 0.79; 95% CI, 0.56-1.12 for premenopausal breast cancer and odds ratio, 0.53; 95% CI, 0.29-0.98 for postmenopausal breast cancer; *P*_{interaction} were 0.89 and 0.30, respectively). An analysis of childhood soy intake and breast cancer risk limited to women with premenopausal breast cancer (86 cases and 134 controls) produced a RR (0.45) and 95% CI (0.20-1.01) similar to that for all women with childhood dietary information. It was not possible to assess the effect of childhood soy intake in women with postmenopausal breast cancer due to small numbers (11 cases and 19 controls).

For childhood, adolescent, and adult soy intake, there was no statistically significant effect modification by family history, age at menarche, age at first live birth, parity, or history of benign breast disease, and the soy-breast cancer associations were similar across subgroups. For women below and above the median adult body mass index in this population (26.3 kg/m^{1.5}), increasing childhood soy intake was similarly related to reduced breast cancer risk (comparing extreme tertiles, RR, 0.36; 95% CI, 0.11-1.15 and RR, 0.39; 95% CI, 0.13-1.22, respectively). However, for both adolescent and adult soy intake, inverse associations were stronger among leaner than heavier women (adolescent intake: RR, 0.62; 95% CI, 0.40-0.96 and RR, 1.02; 95% CI, 0.66-1.59, respectively; adult intake: RR, 0.60, 95% CI, 0.39-0.92 and RR, 0.94; 95% CI, 0.61-1.45, respectively), although the *P*_{interaction} values were not significant for any age group.

Evaluation of the joint influence of childhood and adult diet suggested that soy intake during childhood was inversely associated with breast cancer risk at both low/moderate and high levels of adult intake (Table 3).

Table 3. RR of breast cancer and 95% CI by tertiles of soy intake during both childhood and adulthood

Childhood soy intake* (mother interviewed)	Adult soy intake* (subject interviewed)	
	Low/medium	High
Low		
Cases/controls	35/46	5/4
RR (95% CI)	1.0 (reference)	1.52 (0.30-7.62)
Medium		
Cases/controls	19/34	11/17
RR (95% CI)	0.44 (0.18-1.03)	0.51 (0.18-1.46)
High		
Cases/controls	16/37	10/15
RR (95% CI)	0.36 (0.15-0.86)	0.60 (0.20-1.78)

NOTE: The fully adjusted model is presented. RR are adjusted for study design variables [age at diagnosis (20-39, 40-44, 45-49, ≥50 y), ethnicity (Chinese, Japanese, Filipino), and study center (Hawaii, Los Angeles, San Francisco-Oakland)] and parity/age at first live birth (nulliparous/never pregnant, 1-2 live births/age at first birth ≤20 y, ≥3 live births/age at first live birth ≤20 y, 1-2 live births/age at first live birth ≥21 y, ≥3 live births/age at first live birth ≥21 y, missing), menopausal status at diagnosis (premenopausal, postmenopausal, missing/other), age at menarche (<13 y, ≥13 y, missing/other), family history of breast cancer (yes, no), and personal history of benign breast disease (yes, no, missing).

*Soy intake was stratified as tertiles based on the frequency distribution of intake among controls in each period. Subjects with intake in the low tertile during childhood and intake in the low and middle tertiles during adulthood were used as the reference category.

Table 4. RR of breast cancer and 95% CI by tertiles of soy intake during childhood, adolescence, and adulthood among Asian American women born in the East and in the West

Soy intake*	Born in the East		Born in the West	
	Cases/controls	RR (95% CI)	Cases/controls	RR (95% CI)
Childhood				
Low	17/15	1.0	24/35	1.0
Medium	6/14	0.21 (0.04-1.12)	24/37	0.50 (0.20-1.30)
High †	11/16	0.46 (0.08-2.68)	15/36	0.32 (0.12-0.86)
<i>P</i> _{trend}		0.41		0.03
<i>P</i> _{interaction}				0.41
Adolescence				
Low	133/197	1.0	82/118	1.0
Medium	72/134	0.88 (0.59-1.32)	114/168	1.13 (0.73-1.75)
High †	109/221	0.80 (0.52-1.22)	66/102	0.94 (0.57-1.54)
<i>P</i> _{trend}		0.33		0.60
<i>P</i> _{interaction}				0.90
Adulthood				
Low	126/174	1.0	79/122	1.0
Medium	105/186	0.77 (0.53-1.12)	117/153	1.22 (0.82-1.82)
High †	90/200	0.66 (0.42-1.01)	74/125	0.87 (0.55-1.37)
<i>P</i> _{trend}		0.07		0.37
<i>P</i> _{interaction}				0.33

NOTE: The fully adjusted model is presented. RR are adjusted for study design variables [age at diagnosis (20-39, 40-44, 45-49, ≥50 y), ethnicity (Chinese, Japanese, Filipino), and study center (Hawaii, Los Angeles, San Francisco-Oakland)] and parity/age at first live birth (nulliparous/never pregnant, 1-2 live births/age at first birth ≤20 y, ≥3 live births/age at first live birth ≤20 y, 1-2 live births/age at first live birth ≥21 y, ≥3 live births/age at first live birth ≥21 y, missing), menopausal status at diagnosis (premenopausal, postmenopausal, missing/other), age at menarche (<13 y, ≥13 y, missing/other), family history of breast cancer (yes, no), and personal history of benign breast disease (yes, no, missing).

*Soy intake was stratified as tertiles based on the frequency distribution of intake in each period among all controls, both those born in the East and West. The low tertile were used as the reference category.

†*P* values for trend were calculated by assigning to each tertile the median soy intake for all subjects in the tertile.

However, risk was not reduced with high adult soy intake at any level of childhood soy intake. When both childhood and adult soy intake were put into the same regression model, the inverse association seen for childhood soy intake remained (RR for highest versus lowest tertile, 0.37; 95% CI, 0.17-0.80), whereas no inverse association was seen for adult soy intake (RR, 1.55; 95% CI, 0.71-3.41). Analysis of the joint effects of childhood and adolescent soy intake produced similar results (data not shown).

We conducted several analyses to assess whether a diet high in soy truly protects against breast cancer or is merely a marker of Asian lifestyles that reduce risk. Because Asian American women born in the West are likely to have a more westernized, less Asian lifestyle than those born in the East, we looked for effect modification by place of birth (Table 4). For childhood soy intake, we used the same absolute cutpoints for women born in the East and in the West and found similar reductions in breast cancer risk. For adolescent and adult soy intake, the risk reduction appeared somewhat attenuated for women born in the West, although wide confidence intervals made it difficult to draw firm conclusions. *P*_{interaction} was not significant in any of these analyses.

We also examined the influence on breast cancer risk of cultural and lifestyle practices indicative of westernization and then compared the strength of the associations with that of soy intake. In general, cultural practices characteristic of Asia were associated with reduced risk regardless of whether they referred to childhood, adolescence, or adulthood (Table 5). During childhood, the association between soy intake and breast cancer (RR, 0.40; as noted in Table 2) was stronger than those seen with Asian cultural and lifestyle practices. However,

during adolescence and adulthood, Asian cultural and lifestyle practices were often associated with more of a decrease in breast cancer risk than high soy intake (RR, 0.80 and 0.76, respectively).

To further test whether soy intake was simply an indicator of Asian lifestyle, we added each of the cultural and lifestyle factors that was statistically significantly associated with breast cancer risk, as well as migration history, to each of the three models for soy intake (Table 6). For adolescent and adult intake, adjustment for these cultural and lifestyle practices consistently, although modestly, attenuated the inverse association with soy intake. For adolescent soy intake, the multivariate RR was 0.80 initially and ranged from 0.83 to 0.90 after addition of the cultural/lifestyle variable; for adult soy intake, the multivariate RR was 0.76 initially and ranged from 0.79 to 0.83 after addition. However, the reduced risk associated with childhood soy intake was essentially unchanged. We also added to the three models a measure of migration history, shown previously to predict a 6-fold gradient in breast cancer risk in this migrant population (2). Adjusting for acculturation in this manner had little effect on the point estimate for childhood soy intake (RR, 0.40; 95% CI, 0.18-0.88; *P*_{trend} = 0.03) but weakened the associations with intake later in life (for adolescent soy intake: RR, 0.88; 95% CI, 0.64-1.21; *P*_{trend} = 0.44; for adult soy intake: RR, 0.83; 95% CI, 0.60-1.12; *P*_{trend} = 0.24; Table 5).

Discussion

Soy intake during childhood, adolescence, and adult life were each associated with a decreased risk of breast

cancer. For women in the highest and middle tertiles of childhood intake compared with the lowest tertile, risk was significantly reduced by ~60%. The inverse trend was also significant ($P = 0.03$). The inverse association with childhood soy intake was noted in all three races, all three study sites, and women with and without a family history of breast cancer. Furthermore, this effect of childhood diet was not attenuated by adjustment for soy intake in adolescence or adulthood. Instead, the weaker effects of adolescent and adult diet were eliminated by adjustment for childhood soy intake. These results suggest that soy intake in early life may be especially relevant to breast carcinogenesis.

It has been proposed that soy intake is merely an indicator of Asian lifestyles that reduce breast cancer risk. However, adjustment for the cultural practices significantly associated with breast cancer risk our study did not noticeably weaken the protective effect of childhood soy intake. Because the inclusion of individual cultural and lifestyle practices in the model might not have sufficiently controlled for acculturation, we also adjusted for migration history, shown previously to predict a 6-fold gradient in breast cancer risk in this migrant population (2). Even addition of this variable,

our best measure of acculturation, did not attenuate the association between childhood soy intake and breast cancer risk. These results suggest that soy intake during childhood may itself modulate biological mechanisms.

We believe that our study is the first to explore the role of childhood soy intake in the development of breast cancer. In previous epidemiologic studies examining adolescent intake, breast cancer risk was significantly reduced by ~50% in women with high soy or phytoestrogen intake during this period (15-17). In these studies, the inverse relationship seen with adolescent intake was stronger than that with adult intake and persisted after controlling for adult soy consumption. Studies that have looked only at adult soy intake have reported less consistent results (6), but protective effects have generally been noted in Asian and Asian American populations (14). It is likely that the absolute levels of adult soy intake are higher in Asian and Asian American populations. However, an additional explanation is that adult soy intake is a more reliable indicator of childhood and adolescent soy intake in Asian populations than in non-Asian populations. Indeed, in our study, the inverse association between childhood soy intake and breast cancer was comparable in Asian American women born

Table 5. RR of breast cancer and 95% CI by cultural and lifestyle practices in childhood, adolescence, and adulthood

Measure of acculturation	Childhood (mother interviewed)		Adolescence (subject interviewed)		Adulthood (subject interviewed)	
	Cases/ controls	RR (95% CI)	Cases/ controls	RR (95% CI)	Cases/ controls	RR (95% CI)
Family religion*						
Western	43/59	1.0	98/232	1.0	293/434	1.0
Eastern	42/69	1.17 (0.5-2.5)	368/554	0.64 (0.5-0.9)	238/412	0.88 (0.6-1.2)
Language spoken at home						
English	46/78	1.0	202/302	1.0	300/455	1.0
Asian [†] and English	14/23	0.91 (0.4-2.2)	83/121	0.83 (0.6-1.2)	82/140	0.74 (0.5-1.1)
Asian [†]	37/51	1.06 (0.5-2.4)	306/533	0.75 (0.6-1.0)	211/362	0.76 (0.6-1.0)
Language of newspapers read by adults in the home						
English	44/83	1.0	193/289	1.0	222/327	1.0
Asian [†] /English equally	22/28	1.43 (0.7-3.2)	122/167	1.11 (0.8-1.5)	84/154	0.82 (0.6-1.2)
Asian [†]	24/41	1.34 (0.6-3.0)	257/476	0.87 (0.7-1.1)	107/233	0.71 (0.5-1.0)
Asian language/culture studied in school by children in family						
No	37/64	1.0	233/331	1.0	—	—
Yes	58/88	0.92 (0.5-1.7)	363/635	0.73 (0.6-0.9)	—	—
Grocery store used						
Western	32/56	1.0	149/223	1.0	282/400	1.0
Western/Asian equally	19/46	0.77 (0.3-1.7)	111/183	0.81 (0.6-1.1)	187/310	0.76 (0.6-1.0)
Asian	45/51	1.79 (0.8-3.8)	333/558	0.76 (0.6-1.0)	128/256	0.60 (0.4-0.8)
Friends						
Not Asian/Asian American	14/19	1.0	60/61	1.0	63/73	1.0
Both	19/23	0.62 (0.2-1.8)	107/152	0.76 (0.5-1.2)	205/333	0.76 (0.5-1.1)
Asian/Asian American	64/110	0.52 (0.2-1.3)	430/753	0.58 (0.4-0.9)	329/560	0.70 (0.5-1.0)
Neighborhood						
Not Asian/Asian American	17/23	1.0	53/78	1.0	124/192	1.0
Mixed	19/40	0.88 (0.3-2.4)	108/166	1.10 (0.7-1.8)	227/426	1.05 (0.8-1.4)
Asian/Asian American	61/90	1.13 (0.5-2.8)	435/722	0.96 (0.6-1.4)	196/348	0.86 (0.6-1.2)

NOTE: RR are adjusted for study design variables [age at diagnosis (20-39, 40-44, 45-49, ≥ 50 y), ethnicity (Chinese, Japanese, Filipino), and study center (Hawaii, Los Angeles, San Francisco-Oakland)] and parity/age at first live birth (nulliparous/never pregnant, 1-2 live births/age at first birth ≤ 20 y, ≥ 3 live births/age at first live birth ≥ 21 y, ≥ 3 live births/age at first live birth ≥ 21 y, missing), menopausal status at diagnosis (premenopausal, postmenopausal, missing/other), age at menarche (< 13 y, ≥ 13 y, missing/other), family history of breast cancer (yes, no), and personal history of benign breast disease (yes, no, missing).

*Excludes subjects who reported that they did not practice any religion during specified period.

[†]Asian refers to any Chinese, Japanese, or Filipino dialect.

[‡]For childhood and adolescence, refers to language of newspapers read by parents; for adulthood, refers to language of newspapers read by subject; excludes those who responded that they were not able to read in any language.

Table 6. RR of breast cancer and 95% CI for the highest, relative to lowest, tertile of soy intake during childhood, adolescence, and adulthood after adjustment for indicators of Asian lifestyle

Cultural/lifestyle variable added to model	RR* (95% CI) for high vs low soy intake in childhood	RR* (95% CI) for high vs low soy intake in adolescence	RR* (95% CI) for high vs low soy intake in adulthood
No variable added	0.40 (0.2-0.8)	0.80 (0.6-1.1)	0.76 (0.6-1.0)
Family religion as an adolescent	0.39 (0.2-0.8)	0.83 (0.6-1.1)	0.80 (0.6-1.1)
Language spoken at home during adolescence	0.37 (0.2-0.8)	0.90 (0.7-1.2)	0.80 (0.6-1.1)
Studying Asian language or culture in school during adolescence	0.42 (0.2-0.9)	0.89 (0.6-1.2)	0.80 (0.6-1.1)
Grocery store used as an adult	0.40 (0.2-0.9)	0.87 (0.6-1.2)	0.81 (0.6-1.1)
Friends during adolescence	0.39 (0.2-0.9)	0.89 (0.7-1.2)	0.79 (0.6-1.1)
Migration history [†]	0.40 (0.2-0.9)	0.88 (0.6-1.2)	0.83 (0.6-1.1)

*RR are adjusted for study design variables [age at diagnosis (20-39, 40-44, 45-49, ≥ 50 y), ethnicity (Chinese, Japanese, Filipino), and study center (Hawaii, Los Angeles, San Francisco-Oakland)] and parity/age at first live birth (nulliparous/never pregnant, 1-2 live births/age at first birth ≤ 20 y, ≥ 3 live births/age at first live birth ≤ 20 y, 1-2 live births/age at first live birth ≥ 21 y, ≥ 3 live births/age at first live birth ≥ 21 y, missing), menopausal status at diagnosis (premenopausal, postmenopausal, missing/other), age at menarche (< 13 y, ≥ 13 y, missing/other), family history of breast cancer (yes, no), and personal history of benign breast disease (yes, no, missing).

[†]Categories for migration history: subject born in the West/1-4 grandparents born in the West, subject born in the West/all 4 grandparents born in the East, subject born in the East/all 4 grandparents born in the East/subject lived in West ≥ 8 y, and subject born in the East/all 4 grandparents born in the East/subject lived in West < 8 y.

in the East and the West, whereas the more modest inverse association with adult soy intake was more pronounced in Asian American women born in the East.

Estrogen is known to play an important role in breast carcinogenesis. Both high circulating estrogen levels and postmenopausal estrogen therapy are associated with increased risk of postmenopausal breast cancer (29, 30). Furthermore, most of the adult reproductive, menstrual, and lifestyle factors that influence breast cancer risk, such as age at first birth, parity, age at menarche, age at menopause, and postmenopausal adiposity, likely act through hormone-related mechanisms. Childhood exposures may also affect breast cancer risk through hormonal mechanisms. In a large cohort of Danish women, Ahlgren et al. found associations between breast cancer risk and childhood height, weight, and rate of growth (31). Other studies have reported similar associations (32-35). In addition, several studies have suggested that overweight and obesity during childhood and adolescence decrease the risk of premenopausal breast cancer perhaps independent of their influence on body mass index in the early adult years (33, 35-37).

Studies of Japanese atomic bomb survivors (38) and women who have received radiation treatment for Hodgkin's lymphoma (39) have suggested that breast tissue may be particularly susceptible to carcinogens in the years before its terminal differentiation. One hypothesis for the decreased risk of breast cancer associated with childhood obesity is that exposure to estrogens produced in adipose tissue during this critical period induces earlier mammary gland maturation (33), which, in turn, decreases sensitivity to carcinogens. A diet high in soy early in life may protect against breast cancer through a similar mechanism because several experimental studies have suggested that soy isoflavones have weak estrogenic effects in the breast (40, 41). Animal models also support the theory that early exposure to these phytoestrogens induces earlier differentiation of terminal duct lobules (42, 43) and reduces the incidence and multiplicity of carcinogen-induced tumors (44). In a recent study in Sprague-Dawley rats by Cabanes et al. (45), prepubertal exposure to estradiol and genestein (the isoflavone most abundant in soy) resulted in

persistent up-regulation of the tumor suppressor gene *BRCA1* in the mammary gland. Thus, several plausible mechanisms exist whereby early-life exposure to phytoestrogens can alter breast cancer risk (24).

Although the strength, statistical significance, and internal consistency of our results for childhood soy intake are provocative, our study does have limitations. Our estimate of soy intake is approximate, and because we did not ask about usual portion size, we were not able to perform a detailed analysis based on estimated phytoestrogen intake. The dietary interview did not systematically include sources of the less common phytoestrogens, so we could not assess their effect. In addition, we depended on a mother's recollection of what she usually fed her daughter during childhood. Evidence suggests that a mother's recollection of early-life exposures (46-49), and specifically early diet (50), is reasonably valid. Alternative approaches to investigating early diet, such as collecting information prospectively in childhood or asking adults to recall their childhood eating patterns, may actually be more problematic.

An additional limitation is the reduced number of subjects for whom we could interview mothers about childhood exposures, which decreased statistical power. Although the point estimates for the association between soy intake and breast cancer risk indicate a stronger effect for childhood than adolescent or adult soy intake, the 95% CI around the estimate for childhood intake are quite wide; thus, a weaker effect is possible. Nonetheless, both the RR for high soy intake during childhood, relative to low, and the test for trend reached statistical significance.

The statistical design excluded women ages > 55 years to maximize the number of subjects for whom we could obtain childhood data by interviewing their mothers. Nonetheless, a number of our study participants (61%) had mothers who were deceased or not living in the United States, and the mothers of an additional 16% were not interviewed because either the mother or the daughter declined participation. Therefore, the subset of women for whom we have childhood dietary data might not be representative of the larger number of women included in our population-based study. In

particular, women who were postmenopausal or older at breast cancer diagnosis often had to be excluded from the childhood soy analyses. Although the subset might not be fully representative, the proportion of study participants with childhood dietary data was similar in cases and controls. It is likely that the subjects with childhood information, all of whose mothers were currently living in the United States, were born in the United States or migrated to the United States at a young age and therefore were more westernized. These women would be expected to have a higher absolute risk of breast cancer, lower levels of childhood soy intake, and weaker effects of childhood soy exposure. Therefore, our results in this subset may have underestimated the influence of childhood soy exposure in a more representative Asian American population.

This study also has distinct strengths. We have reported previously a 6-fold gradient in breast cancer risk by migration patterns in these Asian American women (2). This gradient is comparable with the historic international differences in breast cancer rates between Asia and the West. Thus, this migrant population, similar in ethnic background but diverse with regard to lifestyle, facilitates examination of the modifiable lifestyles that contribute to breast cancer risk. Although several measures of acculturation were positively correlated with breast cancer risk, it was striking that adjustment for these measures of acculturation, and for a composite variable representing migration history, did not attenuate the protective effect of childhood soy intake. Therefore, soy may have a biological role in modulating breast cancer risk, and the timing of this exposure may be critical.

Our epidemiologic analysis is the first to clearly support a role for childhood soy intake in the etiology of breast cancer. The contribution of modifiable childhood exposures to breast carcinogenesis has been postulated for decades, but rarely tested, because of the challenges of designing and fielding an appropriate study. Although the results of our single study are not sufficiently robust to serve as the basis for individual dietary modification or public health policy, they suggest the need for a paradigm shift: for the careful examination of the role of childhood exposures in determining breast cancer risk through *in vitro*, animal, and appropriately designed epidemiologic studies.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

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We thank Information Management Services for analytic support, Westat for study management and data preparation, all the study subjects for willingness to participate, and the staff at the three study centers for careful work and enthusiasm. This work was supported in part by the intramural research program of the NIH and the National Cancer Institute.

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Cancer Epidemiol Biomarkers Prev 2009;18:1050-1059.

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