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Dietary isoflavone intake is not statistically significantly associated with breast cancer risk in the Multiethnic Cohort

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Abstract

Given high soy intake and low incidence rates in Asian countries, isoflavones, substances with an estrogen-like structure occurring principally in soybeans, are postulated to be cancer-protective. We examined the association of dietary isoflavone intake with breast cancer risk in 84,450 women (896 *in situ* and 3,873 invasive cases) who were part of the Multiethnic Cohort (Japanese Americans, whites, Latinos, African Americans, and Native Hawaiians) with wide ranges of soy intake. The absolute amount of dietary isoflavone consumption estimated from a baseline food frequency questionnaire was categorized into quartiles, with the top quartile further subdivided to examine high dietary intake. The respective intakes for the quartiles (Q1, Q2, Q3, lower and upper Q4s) were 0-<3.2, 3.2-<6.7, 6.7-<12.9, 12.9-<20.3, and 20.3-178.7 mg/day. After a mean follow-up of 13 years, hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using Cox regression stratified by age and adjusted for known confounders. Linear trends were tested by modeling continuous variables of interest assigned the median value within the corresponding quartile. We observed no statistically significant association between dietary isoflavone intake and overall breast cancer risk (HR [and 95% CI] for upper Q4 vs. Q1: 0.96 [0.85-1.08]; *P*-trend=0.40). While the test for interaction was not significant (*P*=0.14), stratified analyses suggested possible ethnic/racial differences in risk estimates, with a suggestion that higher isoflavone intake may be protective in Latina, African American, and Japanese American women. These results agree with

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Conflicts of interest Contributions by RM were made prior to her position at Purdue Pharma, L.P. The authors have no conflict of interest to declare.

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previous meta-analyses showing no protection at low intake levels but suggesting inverse associations in high-soy consuming populations.

Keywords

isoflavones; breast cancer; ethnicity; prospective cohort

Introduction

Breast cancer remains the second leading cause of cancer death among women in the United States[1]. Despite advances in prevention and control, the incidence of breast cancer varies considerably by race/ethnicity; compared to non-Hispanic whites, women of Asian ethnicity generally have lower age-adjusted incidence rates in the United States[2]. Some of these differences may be attributed to dietary factors, such as the consumption of soy foods in Asian populations. Despite the fact that intake was measured in multiple ways across studies, several meta-analyses suggested a modest protective effect against breast cancer for higher soy consumption in Asian women[3-6]. Soybeans are a rich source of isoflavones, which are hypothesized to be natural estrogen receptor (ER) modulators that possess both estrogen-like and anti-estrogenic properties[7]. Although the consumption of soy foods in the United States is on the rise, differences in intake, as well as in breast cancer incidence, remain between populations that traditionally consume high amounts of soy foods and women of other ethnicities[8]. Many epidemiological studies on soy intake and breast cancer risk involved Asian populations[7, 9, 10] that consumed traditional soy foods including tofu, fermented soybean paste and sprouts. A small number of case-control studies[11-15] have examined the association of dietary isoflavones with breast cancer risk in Asian women according to hormone receptor status, some of which suggested differential influences by ER status, pointing to possible limited protection in ER+ subtypes. Our study examined the association of dietary isoflavone intake with breast cancer risk in *in situ* and invasive cases, as well as by ER status, and in Japanese American, white, Latina, African American, and Native Hawaiian women using population-based, observational data from the Multiethnic Cohort Study (MEC).

Materials and methods

Study population

The MEC was established to investigate the association of lifestyle and genetic factors with chronic disease. Details of the study's design, recruitment methods, response rates, and baseline characteristics have been published elsewhere[16]. Briefly, the cohort consists of 215,251 men and women who were between the ages of 45 to 75 years at the time of recruitment and were selected from five racial/ethnic populations: Japanese Americans, whites, Latinos, African Americans, and Native Hawaiians. Potential participants were identified through drivers' license files from the Department of Motor Vehicles, voter registration lists, and Health Care Financing Administration data files primarily from Los Angeles County, California and the state of Hawaii. Participants completed a mailed 26-page questionnaire in 1993-1996 that included questions on demographic and lifestyle

factors such as physical activity, cigarette smoking, diet, anthropometric measures, personal history of medical conditions, and family history of cancer; as well as reproductive history and exogenous hormone use among women only[16, 17]. Individuals who reported more than one ancestry were assigned to one of the categories according to the following priority ranking: African America, Native Hawaiian, Latino, Japanese American, and white. The institutional review boards at the University of Southern California and the University of Hawaii have approved the study protocol.

Dietary isoflavone intake assessment

The baseline survey included a food frequency questionnaire (FFQ), which asked participants their average use and serving size of specific foods during the last year. For frequency of consumption, participants could select never or hardly ever, 1 time per month, 2-3 times per month, 1 time per week, 2-3 times per week, 4-6 times per week, 1 time per day, or ≥2 times per day. For many items, photographs of three different plated portions were provided to aid with serving size estimation. A calibration study indicated acceptable correlations (Pearson $r = 0.50$ for total isoflavones) between FFQ and 24-h recall based dietary data[17] and estimated the percentages of women classified in opposite quartiles of absolute intake of isoflavones as 9% in the highest quartile (Q4) for the FFQ and the lowest quartile (Q1) for the 24-hour recalls and 2% in Q1 for FFQ and Q4 for recalls. The respective values for nutrient density were 8% and 1%. Total soy product consumption included self-reported intake of tofu, miso, and vegetarian meats, which constituted the majority of soy foods according to the 24-h recalls that were performed when the FFQ was developed. A few additional foods not included in the FFQ, such as soy milk, green soy beans, and soybean sprouts, accounted for only 6% of total isoflavone intake reported in the 24-hour recalls. Daily isoflavone intake (mg/day) was calculated using a food composition table and based on tofu, miso, and vegetarian meats, as well as mixed dishes containing ingredients derived from soy beans. For example, a “stir-fried beef or pork and vegetables, or fajitas” category made up of a combination of recipes, some with soy, was assigned a default isoflavone value. Since concentrations of isoflavones are so low in other food sources, their contribution to total intake can be considered negligible. Measurement-error-corrected isoflavone densities per 4,184 kJ were also calculated, but the results were not substantially different and, therefore, are not shown.

Exclusion criteria

We excluded women if they did not belong to one of the five major ethnic groups listed above (n = 8,050), if they had missing or invalid dietary data (n = 4,611), or if they were diagnosed with breast cancer before the date of the baseline questionnaire (n = 4,787). If a woman was missing menopausal status but was 55 years of age or older at the time of cohort entry, she was coded as postmenopausal (n = 7,358 recoded as postmenopausal). Otherwise, women with missing menopausal status (n = 1,694) were excluded. Women with missing covariate data (n = 15,176), i.e., age at menarche, oral contraceptive use, menopausal hormone use, BMI, age at first live birth, parity, and years of education were also excluded. After all exclusions, 84,550 women were available for analysis.

Follow-up and case identification

Participants' follow-up time began at the completion of the baseline questionnaire (or at age 45 years for the few individuals who had not yet reached age 45 years) and continued to the earliest of the following endpoints: 1) diagnosis of breast cancer, 2) death, or 3) end of follow-up (December 31, 2007). All incident cases of *in situ* or invasive breast cancer [International Classification of Diseases for Oncology (ICD-O-3) code C50] were identified through record linkage to the Hawaii Tumor Registry, the Cancer Surveillance Program for Los Angeles County, and the California State Cancer Registry; all cancer registries are part of the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) program. Deaths within the cohort were determined through annual linkage to state death certificate files in California and Hawaii and periodically to the National Death Index. During a mean follow-up time of 12.5 years (median = 13.7 years), a total of 4,769 women with incident *in situ* (N=896) and invasive (N=3,873) breast cancer were identified.

Statistical analysis

The absolute amount of dietary soy isoflavone consumption (mg/day) was categorized into quartiles (Q1-Q4) for the current analysis. Additionally, the highest quartile category was divided into lower and upper Q4s to evaluate the small group of women who reported very high soy intake. The range of 28.0-160.8 mg/day in the upper Q4 category was similar to consumption levels (26-54 mg/day) described for Japanese populations[8] and to median values of the highest intake categories reported in past studies of Asian populations (>20 mg/day)[4]. Because the distribution of soy consumption varied substantially across ethnic groups, ethnic-specific quartiles for each group were created for stratified analyses. Characteristics of women at cohort entry were compared across quartiles. Since dietary sources of isoflavones included not just soy but also other legumes, Pearson's correlation coefficients were calculated between soy food consumption and total isoflavone intake across ethnic groups to evaluate the differences in the proportion of dietary isoflavones provided by soy food intake. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using Cox proportional hazards models. The lowest intake quartile group served as the reference in all models. Age was the underlying time variable in the Cox regression model, starting with a participant's age at cohort entry to the earliest of the three endpoints mentioned above. Cox regression models included ethnicity (Japanese American, white, Latina, African American, and Native Hawaiian) as a stratum variable and adjusted for age at cohort entry (continuous), body mass index (BMI; <20, 20-<25, 25-<30, ≥30 kg/m^2), age at menarche (≤12, 13-14, ≥15 years), age at first live birth (no children, ≤20, 21-30, or ≥31 years), parity (nulliparous, 1, 2-3, ≥4 children), menopausal status (pre- or postmenopausal or age ≥55 years at cohort entry), education (≤12, >12 years), oral contraceptive use (never, ≥1 mo), menopausal hormone use (no current use/premenopausal, past estrogen, current estrogen/no progesterone; current estrogen with current/past progesterone), family history of breast cancer (no, yes), total energy intake (log-transformed continuous), alcohol consumption (0, >0 g/day), smoking (never, past, current), diabetes (no, yes), and hypertension (no, yes). Although protective in some studies, we did not include physical activity, as covariate because its inclusion did not materially change the risk estimates.

Linear trends were tested by modeling the median values of the corresponding quartile as continuous variables.

Analyses were conducted for all cases and stratified by *in situ* and invasive behavior. Heterogeneity in the risk estimates across ethnic groups, as well as Japanese vs. other ethnic groups combined, was tested by a global Wald test of the cross-product terms for ethnicity and the ethnicity-specific trend variable of total intake or density of dietary isoflavones (assigning the ethnic-specific median values within the corresponding quartiles). Heterogeneity in the risk estimates by ER status was evaluated using a competing risk model, which compares proportional hazards models of ER+ and ER− breast cancer cases by score test[18]. ER− breast cancer cases were censored at their diagnosis age in the ER+ model and ER+ cases were similarly censored in the ER− model. Subgroup analyses were also conducted by BMI status (<25 kg/m^2 vs. ≥25 kg/m^2) and alcohol intake (0 g/day vs. >0 g/day), and for each of the five racial/ethnic groups. In sensitivity analyses, we restricted events to invasive cases, censoring *in situ* cases at the time of death or at end of follow-up; or postmenopausal women only. We also excluded breast cancer cases diagnosed within 2 or 4 years after cohort entry. All statistical analyses were performed in SAS version 9.3 (SAS Institute, Cary, NC) with a two-sided *P* value of <0.05 considered statistically significant.

Results

In the current study population, the quartiles (Q1, Q2, Q3, and lower and upper Q4s) of dietary isoflavone intake at cohort entry were 0-<3.2 (median: 1.7), 3.2-<6.7 (4.8), 6.7-<12.9 (9.1), 12.9-<20.3 (16.0), and 20.3-178.7 (29.6) mg/day, respectively (Table 1). Women differed significantly in demographic and reproductive characteristics, as well as in medical history, across quartiles of dietary isoflavone intake. Women who were Japanese American, Native Hawaiian, or Latina tended to have higher daily intake of isoflavones, as did women who were underweight or of normal weight, had never used oral contraceptives, had ≤12 years of education, had never consumed alcohol or smoked cigarettes, or had been diagnosed with diabetes. On the other hand, women who were obese tended to have lower intakes of isoflavones, as did women who were nulliparous. Across ethnic groups, total soy intake from tofu, miso, and vegetarian meats was highly correlated with total isoflavone intake in Japanese American women (r = 0.83; P <0.0001) reflecting their isoflavone intake primarily from these soy foods, followed by Native Hawaiian (r = 0.80; P <0.0001) and white (r = 0.67; P <0.0001) women. Correlations were lower in African American (r = 0.37; P <0.0001) and Latina (r = 0.23; P <0.0001) suggesting lower reporting of intakes of these individual soy foods and higher consumption of mixed dishes. Of the 3 types of soy foods in the baseline FFQ, Japanese Americans reported much higher soy intake (27 g/day) than other groups. They ate mostly tofu and miso comprising 99% of self-reported soy food intake (g/day), whereas the respective numbers were 97%, 84%, 70%, 64% for Native Hawaiians, whites, Latinas, and African Americans, respectively.

In multivariable models adjusted for all covariates (Table 2), no association was observed for quartiles of absolute dietary isoflavone intake and overall breast cancer risk, with a HR of 0.96 for the highest intake level (*P*-trend = 0.36). Results were similar in sensitivity analyses restricted to postmenopausal women (*P*-trend = 0.56) or to the 3,873 cases of

invasive breast cancer (*P*-trend = 0.24). Excluding cases diagnosed within 2 or 4 years after cohort entry or stratification of women by BMI category or alcohol intake did not materially alter the results.

No heterogeneity in the risk estimates was detected by ethnicity (*P*-interaction = 0.14) or ER status (*P*-interaction = 0.90). In additional, stratified analyses by ethnicity, no statistically significant associations were observed for dietary isoflavone intake and overall breast cancer risk (Table 3). Among Japanese American women who had higher median isoflavone intake than other ethnic groups across quartiles (Table 3), an inverse association between high absolute isoflavone intake and overall breast cancer risk was close to statistical significance (HR for upper Q4 vs. Q1: 0.86 [0.70-1.05]; *P*-trend = 0.06). However, no statistically significant heterogeneity (*P*-interaction = 0.90) was observed in the comparison of Japanese vs. other ethnic groups combined. Similar non-significant inverse associations between the highest intake category and overall breast cancer risk were also seen in Latina (HR for upper Q4 vs. Q1: 0.89 [0.65-1.21]; *P*-trend = 0.41) and African American (HR for upper Q4 vs. Q1: 0.87 [0.68-1.12]; *P*-trend = 0.22) women. Interestingly, Native Hawaiian women showed a non-significant increase in risk for the highest total isoflavone intake group (HR for upper Q4 vs. Q1: 1.45 [1.02-2.07]; *P*-trend = 0.10). Moreover, there was a significantly-positive, dose-response relation between daily isoflavone intake and the 44 ER− breast cancer among Native Hawaiian women (HR for upper Q4 vs. Q1: 3.87 [1.30-11.54]; *P*-trend<0.01). This relationship was attenuated when modeling nutrient density for isoflavone intake (*P*-trend = 0.04; data not shown) despite showing similar risk estimates across quartile categories (HR for upper Q4 vs. Q1: 3.06 [1.15-8.13]). In Latina women, while total isoflavone intake and overall breast cancer risk were not significantly associated, a lower risk of ER+, but not ER- breast cancer, was seen with higher density of isoflavone intake (*P*-trend = 0.02 and 0.68, respectively). No associations with ER+/ER− cancers were observed in Japanese American women or in any of the other ethnic groups.

Discussion

In this prospective cohort study conducted among a multiethnic population with a broad range of dietary intake, we found no statistically significant association between isoflavone intake and overall breast cancer risk. Despite the estrogen-like structure of isoflavones, these null findings persisted irrespective of ER status or when restricted to invasive breast cancers. While the analyses did not demonstrate a statistically significant interaction with ethnicity, stratified analyses suggested possible ethnic differences in risk estimates, in particular, a weak protective association of higher isoflavone intake in some ethnic groups. These results agree with previous meta-analyses showing no association for white populations with low soy intake but protective effects in high-soy consuming Asian countries[4, 5].

While individual studies have reported conflicting results, four meta-analyses[3-6] of mostly case-control and prospective studies across countries and regions generally suggest a protective role of soy against breast cancer in both pre- and post-menopausal women, especially among Asian women with high soy consumption; however, one earlier meta-analysis, when restricted to Asian women, did not support this conclusion[3]. In our present study among mostly (>80%) postmenopausal women with varying soy intake, no

statistically significant association was detected after 13 years of follow up, and no heterogeneity in risk estimates across racial/ethnic groups. Whereas we failed to observe a statistically significant association using FFQ-based dietary intake data, a case-control study[19] nested within the subset of the MEC participants with urine samples observed a lower breast cancer risk in postmenopausal women with higher urinary prediagnostic isoflavone excretion levels. In a comparison of 251 breast cancer cases and 462 matched controls, a significant linear trend test suggested a lower risk for higher levels of daidzein +genistein+equol excretion in all women (OR for Q4 vs. Q1: 0.69 [95% CI: 0.43-1.10]; *P*-trend = 0.04) especially among Japanese American women (OR for Q4 vs. Q1: 0.53 [95% CI: 0.24-1.16]; *P*-trend = 0.003). However, other prospective studies that examined circulating or urinary isoflavones did not consistently observe protective effects[5].

While isoflavone intake at the highest level for Japanese American women in our study was comparable to mean amounts (26-54 mg/day) consumed in Japan[8], overall consumption was much lower, which possibly explains the lack of association. The low isoflavone intake in white women in our study was also similar to levels reported for no-soy-consuming countries[20]. Moreover, it is possible that FFQ-related measurement errors attenuated the association toward the null, largely because the FFQ did not capture soybeans, soymilk, and other food items that constituted a small proportion (6%) of all isoflavones reported in 24-hour recalls during the calibration study. An added problem is the broad use of soy as a component in a variety of food products such as canned tuna and white bread[21, 22], which is not included in the current food composition table. Intake of isoflavones from dietary supplements and modern soy foods, such as soy bars, was also not captured, but they were not common until recent years. Given the difficulty of capturing all soy-containing foods and supplements using FFQs, as well as imprecise estimates of isoflavone intake resulting from mixed dishes with default isoflavone values, the use of biomarkers, such as urinary isoflavone excretion levels, may provide a more accurate measure of total soy consumption. The differences in reproductive and other important characteristics related to breast cancer risk across quartiles of dietary isoflavone intake (Table 1) also suggest that these women are probably different in other unmeasured factors, which may have confounded the potential true relationship. We do not have a plausible explanation for the non-significant increase in breast cancer risk associated with the highest isoflavone intake in Native Hawaiian women, who also had high isoflavone intake largely from soy food intake, other than a possible chance finding. Finally, it has become apparent that timing of soy consumption is very important; animal and case-control studies have shown that soy intake during adolescence may be more important than during adulthood[20, 23]. Therefore, women in Hawaii and California may not have sufficiently exposed to soy early in life to experience benefits at an older age.

Stratified analyses by ER status in the current study suggested possible effect modification by ethnicity. These preliminary findings add to conflicting evidence from case-control studies suggesting differential effects of soy intake by hormone receptor status[11, 12, 15] possibly due to the estrogen-like structure of isoflavones. Our findings, however, should be interpreted with caution given the small sample sizes within ethnic strata and possible chance findings due to multiple comparisons.

There are several strengths to the present study. The multiethnic population allowed comparisons across ethnic groups with a broad range of dietary isoflavone intake. The large sample size and population-based cohort design strengthened the generalizability of the observed overall findings. The prospective study design minimized differential bias in self-reported dietary data. The mean follow-up period was longer than past prospective studies (13 vs. 4-11 years) in Asian countries[5]. There were also important limitations of note. Our estimation of soy intake is not complete. As discussed above, we estimated dietary isoflavone intake principally from consumption of soy foods, such as tofu, miso soup, and vegetarian meat products. However, not all soy foods (e.g., green soybeans, soymilk, health bars, and cereals) were included in the baseline FFQ. Our Japanese American population, consisting largely of the second and third generations of immigrants, probably had different dietary and other lifestyle characteristics from Japanese women in Japan. The smaller sample sizes in stratified analyses by ethnicity or ER status did not allow for robust risk estimates. We also did not have additional subtype information on breast cancer cases, such as progesterone receptor or HER-2 status, to conduct stratified analyses by these characteristics.

In our prospective cohort of mostly postmenopausal women, we observed no statistically significant association between estimated dietary isoflavone intake and overall breast cancer risk across racial/ethnic groups. These results agree with the equivocal findings of past FFQ-based studies evaluating the protective effects of soy consumption against breast cancer[3-6]. Given the measurement errors associated with dietary intake data, use of biomarker measures may clarify the literature by enhancing the assessment of isoflavone exposure in future investigations.

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Table 1

Characteristics of women at cohort entry by quartile (Q1-Q4) of isoflavone intake[1]

Characteristics	Q1	Q2	Q3	Lower Q4	Upper Q4	P-value
N	21,137	21,138	21,138	10,568	10,569	
	1.7	4.8	9.1	16.0	29.6	
Dietary isoflavone intake, *mg/day*	(0.0-<3.2)	(3.2-<6.7)	(6.7-<12.9)	(12.9-<20.3)	(20.3-178.7)	
Ethnicity						<0.0001
Japanese American (N=23,890)	5. 0	20.4	38.4	49.0	49.6	
White (N=21,758)	43.1	29.3	19.4	13.1	9.0	
Latina (N=16,725)	19.2	19.4	18.0	19.5	25.6	
African American (N=15,872)	29.5	23.6	14.6	8.8	6.2	
Native Hawaiian (N=6,305)	3.3	7.3	9.6	9.7	9.5	
Body mass index. kg/m^2						<0.0001
<20	6.8	7.2	8.4	10.2	10.3	
20-<25	36.6	37.9	39.8	41.2	40.8	
25-<30	32.1	31.7	31.0	30.3	29.6	
≥30	24.5	23.2	20.8	18.4	19.3	
Menopausal status						<0.0001
Premenopausal	14.1	16.4	17.4	15.0	13.8	
Postmenopausal[2]	85.9	83.6	82.6	85.0	86.2	
Age at menarche						<0.0001
≤12	51.6	51.1	50.2	49.2	44.9	
13-14	37.6	38.1	38.4	38.2	39.2	
≥15	10.8	10.8	11.4	12.6	15.9	
Parity						<0.0001
No children	14.8	12.6	11.9	12.2	12.2	
1 child	12.6	12.0	10.8	10.3	10.1	
2-3 children	43.4	44.6	46.8	46.1	43.3	
≥4 children	29.3	30.9	30.6	31.4	34.4	
Age at first live birth						<0.0001
No children	14.8	12.6	11.9	12.2	12.2	
≤20	32.4	31.5	27.1	24.1	24.7	
21-30	47.3	49.6	54.1	56.1	55.2	
≥31	5.5	6.4	6.9	7.7	8.0	
Oral contraceptive use						<0.0001
Never	53.0	53.2	56.6	61.1	65.6	
Ever (at least 1 month)	47.1	46.8	43.4	38.9	34.4	
Menopausal hormone therapy						<0.0001
No current use or premenopausal	52.1	53.6	54.0	53.2	55.5	
Past estrogen use	17.1	16.3	15.1	16.4	15.2	
Current estrogen with no progesterone use	14.6	13.9	13.8	12.9	13.5	
Current estrogen with	16.2	16.2	17.1	17.5	15.9	

Characteristics	Q1	Q2	Q3	Lower Q4	Upper Q4	P-value
Current/past progesterone use						
Family history of breast cancer						<0.0001
No	88.1	89.1	88.8	88.6	90.1	
Yes	11.9	10.9	11.2	11.4	9.9	
Education, years						<0.0001
≤12 years	40.0	41.3	43.7	46.5	51.5	
≥12 years	60.0	58.7	56.3	53.5	48.5	
Alcohol consumption						<0.0001
0 g/day	54.9	57.7	62.7	66.8	69.7	
≥0 g/day	45.1	42.3	37.4	33.2	30.3	
Smoking						<0.0001
Never	49.2	51.9	56.9	62.2	64.2	
Past	33.2	32.3	29.3	26.6	26.0	
Current	17.7	15.9	13.8	11.2	9.9	
Diabetes, *Yes*	9.9	9.8	10.5	11.3	12.3	<0.0001
Hypertension, *Yes*	38.0	37.4	37.25	37.2	37.3	0.52

[1]Data are presented as percentage within each quartile category or mean ± SD except for dietary isoflavone intake, which is shown as median (range). Percentages may not add to 100 due to rounding. Univariate comparisons across quartile categories were performed using chi-square test (categorical variables) or analysis of variance (continuous variable).

[2]Postmenopausal or age ≥55 years at baseline.

Table 2

Risk of breast cancer by quartile (Q1-Q4) of dietary isoflavone consumption[1]

Total isoflavone intake, *mg/day*		**All (*in situ* and invasive) cases (N = 4,769)**			**Postmenopausal women only (N = 4,112)**			**Invasive breast cancer only (N = 3,873)**			**ER+ only[2] (N = 2,393)**			**ER- only[2] (N = 625)**		
	Median (range)	**Cases (N)**	**HR**	**95% CI**	**Cases (N)**	**HR**	**95% CI**	**Cases (N)**	**HR**	**95% CI**	**Cases (N)**	**HR**	**95% CI**	**Cases (N)**	**HR**	**95% CI**
Q1	1.7 (0.0-<3.2)	1,162	1.00	--	1,009	1.00	--	975	1.00	--	609	1.00	--	155	1.00	--
Q2	4.8 (3.2-<6.7)	1,174	0.99	0.91-1.08	1,014	1.01	0.92-1.11	958	0.97	0.88-1.06	607	0.99	0.88-1.11	162	1.07	0.85-1.34
Q3	9.1 (6.7-<12.9)	1,242	1.00	0.92-1.10	1,048	1.01	0.92-1.12	984	0.96	0.87-1.07	596	0.95	0.83-1.07	155	1.07	0.84-1.37
Lower Q4	16.0 (12.9-<20.3)	605	0.96	0.86-1.07	520	0.96	0.85-1.08	488	0.92	0.81-1.05	291	0.90	0.77-1.06	81	1.16	0.85-1.57
Upper Q4	29.6 (20.3-178.7)	586	0.96	0.85-1.08	521	0.98	0.86-1.12	468	0.92	0.81-1.05	290	0.94	0.80-1.12	72	1.06	0.76-1.47
P-trend[1]			0.40			0.56			0.24			0.44			0.77	

[1] Hazard ratio and 95% confidence interval (CI) adjusted for ethnicity (Japanese American, White, Latina, African American, and Native Hawaiian included as a strata variable), age at cohort entry (continuous), body mass index (BMI; <20, 20-<25, 25-<30, or ≥30 kg/m^2), age at menarche (≤12, 13-14, ≥15 years), age at first live birth (no children, ≤20, 21 -30, or ≥31 years), parity (nulliparous, 1, 2-3, ≥4 children), menopausal status (premenopausal, postmenopausal or age ≥ 55 years at cohort entry), years of education (≤12, >12 years), oral contraceptive use (never, ≥ 1 month use), menopausal hormone use (no current use or premenopausal; past estrogen use, current estrogen with no progesterone use; current estrogen with current/past progesterone use), family history of breast cancer (no, yes), total energy intake (log-transformed continuous), alcohol consumption (0, > 0 g/day), smoking (never, past, current), diabetes (no, yes), and hypertension (no, yes). Linear trends were tested by modeling continuous variables of interest assigned the median value within the corresponding quartile. Linear trends were tested by modeling continuous variables assigned the median value within the corresponding quartile.

[2] Estrogen receptor (ER) status $^+$ or $^-$.

Table 3

Risk of breast cancer (*in situ* and invasive) by ethnicity-specific quartile (Q1-Q4) of dietary isoflavone consumption[1]

	Japanese American (N=23,890)				White (N=21,758)				Latina (N=16,725)				African American (N=15,872)				Native Hawaiian (N=6,305)			
	Median (range)	Cases (N)	HR	95% CI	Median (range)	Cases (N)	HR	95% CI	Median (range)	Cases (N)	HR	95% CI	Median (range)	Cases (N)	HR	95% CI	Median (range)	Cases (N)	HR	95% CI
Total isoflavone consumption, *mg/day*																				
Q1	5.0 (0.1-<7.1)	359	1.00	--	0.9 (0.0-1.8)	312	1.00	--	1.7 (0.0-<3.2)	194	1.00	--	1.1 (0.0-<2.0)	238	1.00	--	3.4 (0.1-<5.2)	96	1.00	--
Q2	9.0 (7.1-<11.4)	427	1.16	1.00-1.33	2.8 (1.8-<3.9)	315	1.05	0.90-1.23	4.8 (3.2-<7.0)	175	0.92	0.75-1.14	3.0 (2.0-<4.2)	207	0.86	0.71-1.03	7.0 (5.2-<9.2)	109	1.14	0.86-1.50
Q3	14.5 (11.4-<18.9)	386	1.02	0.88-1.19	5.4 (3.9-<7.7)	324	1.10	0.94-1.29	9.9 (7.0-<14.7)	161	0.88	0.70-1.10	5.5 (4.2-<7.5)	225	0.92	0.76-1.11	11.6 (9.2-<15.4)	124	1.26	0.95-1.67
Lower Q4	22.4 (18.9-<28.0)	212	1.12	0.93-1.34	9.2 (7.7-<11.8)	146	1.02	0.83-1.25	18.6 (14.7-<24.0)	71	0.80	0.60-1.07	8.9 (7.5-<11.3)	80	0.65	0.50-0.84	18.4 (15.4-<23.7)	47	0.95	0.66-1.38
Upper Q4	36.8 (28.0-160.8)	163	0.86	0.70-1.05	17.3 (11.8-114.1)	148	1.06	0.86-1.30	34.8 (24.0-178.7)	74	0.89	0.65-1.21	17.4 (11.3-112.3)	107	0.87	0.68-1.12	33.5 (23.7-165.8)	69	1.45	1.02-2.07
P-trend[1]		0.06				0.78				0.41				0.22				0.10		
P-heterogeneity[2]										0.14										

[1]Hazard ratio and 95% confidence interval (CI) adjusted for ethnicity (Japanese American, white, Latina, African American, and Native Hawaiian included as a strata variable), age at cohort entry (continuous), body mass index (BMI; <20, 20-<25, 25-<30, or ≥30 kg/m^2), age at menarche (≤12, 13-14, ≥15 years), age at first live birth (no children, ≤20, 21 -30, or ≥31 years), parity (nulliparous, 1, 2-3, ≥4 children), menopausal status (premenopausal, postmenopausal or age ≥ 55 years at cohort entry), years of education (≤12, >12 years), oral contraceptive use (never, ≥ 1 month use), menopausal hormone use (no current use or premenopausal; past estrogen use, current estrogen with no progesterone use; current estrogen with current/past progesterone use), family history of breast cancer (no, yes), total energy intake (log-transformed continuous), alcohol consumption (0, > 0 g/day), smoking (never, past, current), diabetes (no, yes), and hypertension (no, yes). Linear trends were tested by modeling continuous variables of interest assigned the median value within the corresponding quartile. Linear trends were tested by modeling continuous variables assigned the median value within the corresponding quartile.

[2]Heterogeneity in the risk estimates across ethnic groups was tested by a global Wald test of the cross-product terms for ethnicity and the ethnicity-specific trend variable of total intake or density of dietary isoflavones (assigning the ethnic-specific median values within the corresponding quartiles).