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Soy isoflavone intake is associated with risk of Kawasaki disease

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Abstract

Kawasaki disease (KD) is an acute vasculitis affecting children. Incidence of KD varies according to ethnicity and is highest in Asian populations. Although genetic differences may explain this variation, dietary or environmental factors could also be responsible. The objectives of this study were to determine dietary soy and isoflavone consumption in a cohort of KD children just before disease onset and their mothers' intake during pregnancy and nursing. We tested the hypothesis that soy isoflavone consumption is associated with risk of KD in US children, potentially explaining some of the ethnic-cultural variation in incidence. We evaluated soy food intake and isoflavone consumption in nearly 200 US KD cases and 200 age-matched controls using a food frequency questionnaire for children and in their mothers. We used a logistic regression model to test the association of isoflavones and KD. Maternal surveys on soy intake during pregnancy and nursing showed no significant differences in isoflavone consumption between groups. However, we identified significantly increased KD risk in children for total isoflavone (odds ratio [OR], 2.33; 95% confidence interval [CI], 1.37–3.96) and genistein (OR, 2.46; 95% CI, 1.46–4.16) intakes, when comparing high soy consumers vs nonconsumers. In addition, significantly increased KD risk occurred in Asian-American children with the highest consumption (total isoflavones: OR, 7.29; 95% CI, 1.73–30.75; genistein: OR, 8.33; 95% CI, 1.92–36.24) compared to whites. These findings indicate that childhood dietary isoflavone consumption, but not maternal isoflavone intake during pregnancy and nursing, relates to KD risk in an ethnically diverse US population.

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Conflict of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.nutres.2016.04.002>.

Keywords

Autoimmune; Isoflavones; Kawasaki disease; Mucocutaneous lymph node syndrome; Phytoestrogens

1. Introduction

Kawasaki disease (KD) is the leading cause of acquired heart disease in children in most developed countries including the United States [1]. Peak age incidence of KD occurs in children younger than 5 years, but cases can occur even in adolescence. In the United States alone, approximately 5500 cases were estimated in 2009 with only passive surveillance [2], and based on system dynamics modeling simulations, there will be an average of 6200 new patients each year with an acute KD [3]. Kawasaki disease is a life-threatening acute vasculitis that diffusely involves multiple organ systems in children but has a predilection for involvement of the coronary arteries [4]. Acute inflammation within the coronaries can result in arterial dilation and aneurysm formation with subsequent development of stenosis during a chronic convalescent phase. Thus, KD leads to significant morbidity in a relatively young population.

Even after 50 years of research, the etiology for this disease remains elusive, and the risk factors still need to be defined. Many consider KD an autoimmune phenomenon, and thus, anti-inflammatory high-dose intravenous immunoglobulin provides the mainstay therapy. The prevailing theories for causation include antigen presentation followed by an autoimmune response in genetically susceptible individuals [5]. Asian ethnicity is the primary risk factor. Kawasaki disease incidence in Japan exceeds 220 per 100 000 children, greater than 10 times the rate in the United States [6]. Eastern Asian countries including Korea and Taiwan [7] also show remarkably high KD incidence compared to nations with populations of predominantly European descent [8]. The high incidence rate persists in Japanese descendant children living in the United States [9]. Hypotheses implicating genetic differences among populations as the defining factors for ethnic variation in incidence predominate [7]. Genetic studies have identified ethnic differences in HLA and CD40 loci in KD populations. However, these differences do not account for the extreme variation in KD incidence [10]. Environmental agents or toxins have historically been considered as potential KD triggers or risk factors [11]. More recent theories suggest that environmental factors borne by tropospheric wind currents emanating from central Asia and extending over Japan, Hawaii, and then the US Pacific Coast play an important role for in the pathogenesis [12].

We recently proposed a hypothesis that isoflavones in soy alter immune response in young children and cultural differences in diet therefore may explain in part the ethnic differences in KD incidence [13]. The hypothesis is supported by mechanistic data on effects of the soy isoflavone genistein [14,15,16] and by epidemiological studies conducted in Hawaii, which show ethnic group-based associations between soy consumption and KD incidence [9,17,13]. However, the epidemiologic analysis did not directly consider soy consumption in KD patients but extrapolated data from the general population. Accordingly, we tested the hypothesis that soy isoflavone consumption is associated with risk of KD in a US-based

cohort by performing nutritional assessments in children with KD. We also extended the hypothesis to include maternal soy consumption during pregnancy and lactation as risk factors for KD.

2. Methods and materials

2.1. Study design and subjects

We conducted a case-control study in the Seattle Children's Hospital (SCH) Kawasaki cohort, which included all patients diagnosed and seen in clinic between January 2000 and July 2014 and treated and/or followed at the SCH and their mothers. This study was conducted according to the guidelines laid down in the Declaration of Helsinki, and all procedures involving human subjects/patients were approved by the SCH Institutional Review Board number 11897. Written informed consent was obtained from all subjects/patients. This study population represented a portion of a previously described cohort enrolled for genotype analyses. All patients were diagnosed according to the American Heart Association guidelines for both complete and incomplete KD [18]. Child and maternal diet surveys were distributed to families either in clinic or by mail. Parents were instructed to report on dietary intakes for a 3-month period before initial symptoms (reference date) for KD. In attempt to enroll a comparison group within a similar age range, the control subjects were children and their mothers approached in general pediatric cardiology clinic. These subjects were seen for symptoms and signs and found to have no heart disease (eg, innocent murmur) or for minor defects not requiring medical, surgical, or nutritional intervention. The control group completed surveys in clinic or returned them by mail. This group was instructed to report on dietary intakes for the preceding 3months. Although our main interest was reported soy intake, both groups were informed that we were evaluating the role of diet in KD, but not that we were specifically evaluating a role for soy. Of the 522 KD patients who met the American Heart Association diagnostic criteria, 22 were lost to follow-up or we had incorrect or outdated contact information. We distributed surveys to 500 KD patients and their mothers, and 181 returned the surveys. We approached 258 controls meeting our criteria, and 193 completed the surveys (Fig. 1).

2.2. Dietary data collection

Mother's intakes of genistein and total isoflavone (sum of genistein, daidzein, and glycitein) intakes were estimated from mothers' recall of soy intake during pregnancy and while breast-feeding using a validated soy food frequency questionnaire (FFQ) [19]. Soy intake in the children was assessed using the Child Nutritional Intake Survey, an FFQ developed in collaboration with the Nutrition Assessment Shared Resource of the Fred Hutchinson Cancer Research Center, Seattle, Washington. The Child Nutritional Intake Survey was adapted from the Women's Health Initiative FFQ [20]. It was modified to reflect foods commonly consumed by children (eg, infant formula added and alcoholic beverages removed) and soy foods (eg, soy-based "meats," "dairy," and beverages). In addition, the length of the questionnaire was shortened (from more than 120 to 89 line items), primarily by collapsing similar foods into single line items (eg, "regular breakfast sausage, bacon, hot dogs, and lunch meats" listed as a single line item instead of 4 separate line items for "bacon and breakfast sausage," "regular hot dogs and sausage such as bratwurst and chorizo",

“lunch meats such as ham, turkey, and low-fat bologna”, and “all other lunch meats such as bologna, salami, and Spam”).

Eleven questions related to soy foods were imbedded within the total of 89 line items. They included the following line items: “soy-based ‘meats,’ including breakfast sausage, bacon, hot dogs, burgers, and lunch meats, such as Yves or Lightlife”; “soy-based chicken nuggets”; “tofu or tempeh”; “soy-based cheeses, including soy cream cheese”; “soy yogurt”; “cooked soybeans”; “soy-based sour cream”; “soy-based mayonnaise, such as Vegenaïse”; “soy ice cream”; “soy milk, including milk on cereal”; and “soy-based baby formula.” Total number of servings per week of each soy-containing food was calculated. Total isoflavone and genistein content of each food was determined as described previously [19]; serving sizes for children younger than 2 years were defined as half the serving size for adults and children older than 2 years. Sensitivity analyses were carried out by evaluating the difference in point estimates with and without dividing serving sizes in half for children younger than 2 years ($n = 22$ soy consumers; 12 cases). As results were very similar, only data obtained using the halved totals for this age group were analyzed. In both mothers and children, weekly isoflavone and genistein intakes were totaled across all soy-containing foods. Foods with missing values were omitted from totals. Although the survey provided information for multiple dietary variables, only those related to soy consumption were evaluated in detail.

2.3. Statistical analyses

Total soy isoflavones and genistein specifically were our exposures of interest. Weekly total isoflavone and genistein intakes were categorized into 3 groups based on intakes among controls. We used soy nonconsumers as a reference group and divided consumers into 2 groups based on the control cohort median intake value. Those with intake below the median were designated as low-soy consumers, whereas those above the median were high-soy consumers. Group assignments for Kawasaki cases using the median value for controls were made after category cutoffs were determined for controls.

We used a logistic regression model to test the association of total isoflavones and genistein in mothers of KD cases and controls, adjusted for ethnicity [21]. Models testing these associations among children were further adjusted for age and sex. Self-reported food allergies or intolerances (categories included peanuts, other nuts, soy, wheat, fish, shellfish, citrus, and “other”) were assessed as potential confounders but were not significant in any models and therefore not included as an adjustment variable. Because of small numbers of observations in some cells, continuous models using intake of isoflavones and genistein (milligrams per week) were also performed. Because KD incidence differs by ethnicity, risks were evaluated using the same models and procedures in stratified analyses for whites and Asians. To evaluate potential bias due to the length of time between reference date and completion of dietary questionnaires by cases, we performed sensitivity analysis using the same procedures for the main analyses with data from recently diagnosed cases only (2 years since diagnosis) [22]. Further sensitivity analyses were performed using the same models to assess intakes of “white rice, noodles, and other grains,” to evaluate whether co-consumption confounded the relationship between intakes of soy isoflavones and KD incidence among Asians. The 2-sided P value for statistical significance was set at less than .

05. Analyses were performed using Stata statistical software (v13.0; Stata Corp, College Station, TX, USA).

3. Results

Characteristics of KD cases and controls by category of isoflavone intake are given in Table 1. Race is recorded from self-report on the survey. Overall, age of KD case at reference date was slightly younger (4.0 ± 3.7 vs 5.2 ± 4.2 ; $P < .01$), and cases were more likely to be male (61% vs 51%; $P = .03$). Both cases and controls tended to be predominantly white (65% and 77% for cases and controls, respectively) with slightly more cases tending to be of Asian descent (17% vs 11%), although cases and controls did not differ statistically significantly by ethnicity ($P = .20$). The Asian population was grouped from multiple ethnicities, including primarily Chinese, Korean, and Japanese. Medians and interquartile ranges for total isoflavone and genistein intakes for both mothers and children are given in Table 2, whereas mean values are given in Supplementary Table S1. Intake was very similar across the mothers of KD cases and controls. Distribution of total isoflavone intake by KD cases and controls is presented graphically in Fig. 2A for all children and in Fig. 2B and C for white and Asian children, respectively. More than 50% of children in both groups consumed no soy, accounting for a median of 0. However, the mean isoflavone intake was more than double for children with KD compared to controls, particularly among Asians (Supplementary Table S1).

3.1. Association of total isoflavone and genistein intake with KD

When looking at intake of total isoflavones and genistein among mothers during pregnancy or while breast-feeding, there were no significant associations between isoflavone intake and KD risk in children (data not shown). Among children, there was a significantly increased risk for both total isoflavone (odds ratio [OR], 2.33; 95% confidence interval [CI], 1.37–3.96) and genistein (OR, 2.46; 95% CI, 1.46–4.16) intakes among high consumers compared to soy nonconsumers (Fig. 3). The P for trend over the 3 categories was statistically significant (P for trend $< .004$ for isoflavones and $< .002$ for genistein). Point estimates were slightly stronger when analyses were restricted to cases who were diagnosed within 2 years of completing the dietary intake data for total isoflavones ($n = 76$ cases; OR, 2.61; 95% CI, 1.38–4.92) and genistein (OR, 3.02; 95% CI, 1.60–5.69; P for trend $< .002$ for both). Continuous models were not statistically significant.

To evaluate whether other foods typically consumed with soy confounded the relationship between soy intake and KD incidence, a sensitivity analysis was carried out assessing the association of the line item “white rice, noodles, and other grains” (servings per week) with KD among Asian children. Odds ratios for the second and third tertiles of white rice intakes were 0.77 (95% CI, 0.09–6.61) and 0.51 (95% CI, 0.08–3.36), respectively.

3.2. Stratified analysis by white/Asian ethnicity

Isoflavone and genistein intakes for mothers and children stratified by ethnicity are given in Table 3 (medians) and Supplementary Table S2 (means), and distribution of total isoflavone intake is presented in Fig. 1B and C for white and Asian children, respectively. There were

no significant differences in KD risk among children when evaluating total isoflavone or genistein intakes in their mothers stratified by ethnicity, during pregnancy or while breast-feeding, or by category of intake (data not shown).

When evaluated by category of intake among children stratified by ethnicity, there was a statistically significant 7- and 8-fold increased risk of KD among Asian children in the highest category of total isoflavone and genistein intakes, respectively (total isoflavones: OR, 7.29; 95% CI, 1.73–30.75; genistein: OR, 8.33; 95% CI, 1.92–36.24; Table 4). There was also a statistically significant increased risk with increasing isoflavone and genistein intakes across categories (*P* for trend <.007 and <.005, respectively) and an increased risk when evaluating intake as a continuous variable as milligrams per week (total isoflavones: OR, 1.55; 95% CI, 1.11–2.17; genistein: OR, 1.61; 95% CI, 1.10–2.37). Sensitivity analyses were performed to evaluate the potential impact of recall error or bias on our study results. Restricting analyzed data to those obtained from cases diagnosed within 2 years of dietary intake collection did not alter the results other than reducing subject numbers and thereby broadening CIs. For instance, the data restriction resulted in suggestion of greater risk among Asian children; the reduction of the sample size (*n* = 31; 10 cases) resulted in wide CIs (total isoflavones: OR, 18.10; 95% CI, 1.50–218.14; genistein: OR, 19.08; 95% CI, 1.60–227.18; *P* for trend <.02 for both).

4. Discussion

We report for the first time an association between soy isoflavone intake and KD in a case-control study. Thus, we accept our original hypothesis. When compared to soy nonconsumers, the odds of KD were 2 to 2½ times greater among children in the highest category of total isoflavone and genistein intakes. The odds were 7 to 8 times greater among children of Asian descent in the highest category of total isoflavone and genistein intakes, which were higher than among whites.

Kawasaki disease likely results from interactions of multiple genes and environmental factors. The current study tested a novel hypothesis implicating a dietary component—soy isoflavones, predominantly genistein—as one of the susceptibility factors for KD. The biological activity of genistein as an inhibitor of protein tyrosine kinase supports the basis for this hypothesis. This kinase regulates signaling through the Fc-γ receptors, which have been repeatedly identified by genetic studies as important susceptibility factors for KD [23,10,24]. The Fc-γ receptors, which bind antibody complexes on inflammatory cell surfaces, play an important role in regulation of immune response. Genistein interacts with the signaling portion of these receptors, modulating their activity and changing the balance between immune cell activation and inhibition [25,26,27]. Our data support the contention that dietary isoflavones are not a requirement or a trigger but do increase KD risk in children consuming them. Accordingly, among the cases, more than half the patients consumed either no or very low soy in the 3 months before developing KD. However, our data show that the distribution and range of soy isoflavone consumption among the cases differ substantially from the control group, with the overall KD population consuming soy foods at a higher frequency.

Kawasaki disease shows substantially higher prevalence in Asian populations. Therefore, we additionally stratified by ethnicity to reduce the possibility of selection bias. Our data suggest that we recruited proportionally equivalent ethnic composition in the control and case groups and that ethnicity was not a confounding factor for our overall study. Although we had comparatively few ethnic Asian KD children and mothers within both groups compared to white, we explored associations between isoflavone consumption and KD specifically among Asians. Families throughout Asia typically add tofu and other isoflavone-containing foods to complement the infant breast-feeding or formula beginning at 4 to 6 months [28]. Tofu-fed infants show high concentrations of isoflavones in plasma and urine, concentrations which can exceed those found in Asian adults eating soy [29]. The most detailed reporting for soy consumption in children comes from Japan, and such statistics are unavailable for most other Asian countries. The Japanese National Nutritional Survey (1995–2002) showed that Japanese children by age 1 year consume approximately 60% of the average daily soy and isoflavones ingested by adults between the ages of 20 and 40 years [30]. Kawasaki disease peak incidence occurs in Japanese children between 6 and 11 months old, plateaus, and then slowly decreases with advancing age [6]. Our exploratory analyses, despite the small sample size, suggest that isoflavone intake is associated with greater risk in Asians than in whites.

Conducting epidemiologic studies in orphan disease populations such as KD poses considerable challenges to investigators. The relatively large sample size is an important strength of our study. We also used a comprehensive questionnaire for assessing subjects' diets. In addition, we performed this investigation in an ethnically heterogeneous US population displaying variation in soy consumption. The study would not be as feasible if performed in an Asian country such as Japan or China, where soy consumption remains high in most of the population.

Although we used fairly standard case control methodology, the retrospective nature of the dietary data collection represents the main limitation of this study. However, the optimal design, a classic prospective cohort study, would not be feasible considering the relatively low KD incidence (~ 20 per 100 000 children) in the United States. Thus, we instead performed a classic case-control analysis using parental recall of diet just before the acute KD episode. Ideally, the survey would be performed in the immediate period either before or within the few weeks after the reference period. Our prior experience with KD and survey response indicate that such data collection would take many years to achieve sufficient numbers for adequate statistical power. With regard to potential reporting bias, the subjects were blinded to the singular purpose of the study. Furthermore, soy foods were a minor component of the children's food questionnaire and were embedded throughout the questionnaire in the relevant food group categories (eg, protein foods, beverages, dairy substitutes). As other foods are commonly consumed with soy foods among Asian populations, we additionally analyzed the association of the line item "white rice, noodles, and other grains" with KD and found no association, supporting the hypothesis that the association between soy foods and KD is stronger than that with other foods in a more Asian diet. Recall bias is also a potential limitation. Retrospective surveys are dependent on recall but have been used as a cornerstone for KD research [31,32,33,7]. Subject number is considerably higher in our study than in many of those previous studies [31,32] and included

a control group, thereby reducing potential impact of recall bias. Cases and controls were also seen in the same clinic by the same providers reducing potential discrepancies in socioeconomic class. As noted in methods, the controls did not have heart diseases which would require modifications in diet. Ideally, we would have matched controls to cases 1:1 according to age, ethnicity, and sex. However, precise matching to all these parameters was not possible logistically. Instead, we relied on random selection of the control group, which yielded a slight discrepancy in age compared to cases, although sex and ethnicity were not significantly different. Finally, we tested the potential impact of recall error by performing sensitivity analyses using cases reporting within 2 years of the reference period. In fact, the analyses in those patients show an even stronger association between KD and soy/isoflavone consumption, although the CIs are wide due to the decrease in subject number and statistical power.

The study also could be impacted if the control group, in particular, randomly reported lower isoflavone intakes than the general population. High-quality isoflavone intake for children in the United States is not available in the literature. However, our reported isoflavone intakes for the mothers are similar to those provided in large multiethnic reports for US women [34]. The study was not powered to determine if these associations were affected by age. Kawasaki disease before age 6 months was rare (<4%) in our population. Therefore, we could not perform further age-related analyses due to limited power, although isoflavones could be introduced through soy-based formula or very high maternal intake in this young age group. Age analyses may be important, as some prior data support the hypothesis that soy consumption in adolescence, particularly in Asian populations, may be protective against breast cancer. However, that hypothesis has not really been tested for isoflavone exposure in infancy and early childhood.

Our data support our novel hypothesis that soy consumption is a susceptibility factor for KD in childhood, but maternal soy intake is not associated with KD risk. Biological studies implicate isoflavones as an active ingredient in soy that modifies the immune system. However, it is conceivable that soy proteins contain antigens that could also affect immune responses. The data support the need for further observation, caution with respect to soy consumption in childhood, and a more thorough evaluation of isoflavone effects on child cardiovascular health.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

CI confidence interval

FFQ	food frequency questionnaire
KD	Kawasaki disease
OR	odds ratio
SCH	Seattle Children's Hospital

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Fig. 1.
Enrollment for nutritional surveys in KD case and control cohorts.

Fig. 2. Distribution of total isoflavone intake among children (milligrams per week) for Kawasaki cases ($n = 181$) and controls ($n = 193$). A, Overall population ($n = 374$). B, Whites ($n = 274$). C, Asians ($n = 51$). For ease of presentation, 2 data points were omitted from graphs but were included in all analyses (1 Asian control: 778 mg/wk, and 1 white case: 1100 mg/wk).

Fig. 3.

Odds ratios for KD among children derived from logistic regression. Soy nonconsumers, reference group ($n = 122$ controls; $n = 95$ cases); low consumers, total isoflavone intakes below the median ($n = 34$ controls; $n = 28$ cases); high consumers, total isoflavone intakes above the median ($n = 37$ controls; $n = 58$ cases). All analyses were adjusted for ethnicity, age, and sex. The P for trend over the 3 categories was statistically significant (P for trend $< .004$ for isoflavones and $< .002$ for genistein).

Table 1

Characteristics of Kawasaki cases and controls overall and by category of isoflavone intake

Characteristic	Overall		<i>p</i> ^a		Soy nonconsumers		<i>p</i> ^a		Low consumers ^b		<i>p</i> ^a		High consumers ^b		<i>p</i> ^a	
	Controls (n = 193)	Cases (n = 181)	Controls (n = 122)	Cases (n = 95)	Controls (n = 35)	Cases (n = 28)	Controls (n = 36)	Cases (n = 58)	Controls (n = 36)	Cases (n = 58)	Controls (n = 36)	Cases (n = 58)	Controls (n = 36)	Cases (n = 58)	Controls (n = 36)	Cases (n = 58)
Age (y), mean (SD)	5.2 (4.2)	4.0 (3.7)	<.01	4.4 (4.3)	4.0 (3.5)	.41	6.6 (4.1)	3.1 (1.6)	<.01	6.4 (3.6)	4.6 (4.6)	.08	6.4 (3.6)	4.6 (4.6)	.08	6.4 (3.6)
Sex (% male)	51	61	.03	52	68	.01	49	50	.92	39	53	.16	39	53	.16	39
Ethnicity (%) ^c			.20			.53			.20			.08			.20	
White	77	65		75	79		88	75		72	52		72	52		72
Asian	11	17		10	7		6	11		19	34		19	34		19
Other ^d	12	14		15	14		6	14		8	14		8	14		8

^aSignificance between cases and controls within each category.

^bSoy nonconsumers, reference group; low consumers, total isoflavone intakes below the median; high consumers, total isoflavone intakes above the median.

^cPercentages represent totals for controls and cases separately.

^dOther ethnicity includes 22 mixed races, 10 African Americans, 3 Native Americans, 1 Pacific Islander, and 13 not indicated.

Table 2

Total isoflavone and genistein intakes (milligrams perweek) for Kawasaki cases and controls and theirmothers

Isoflavone intake^a	Controls	Kawasaki
Mothers		
During pregnancy	n = 193	n = 181
Total isoflavones	4.2 (0–44.9)	6.5 (0.1–54.1)
Genistein	2.1 (0–22.0)	3 (0–22.7)
While breast-feeding ^b	n = 158	n = 157
Total isoflavones	8.4 (0.1–52.7)	11.4 (0.1–55.1)
Genistein	4.5 (0–26.5)	5.8 (0–25.9)
Children	n = 193	n = 181
Total isoflavones	0 (0–9.0)	0 (0–26.7)
Genistein	0 (0–4.7)	0 (0–13.0)

Values are expressed as median (interquartile range).

^aTotal isoflavones = sum of genistein, daidzein, and glycitein.^bNot all mothers breastfed; rates of breastfeeding infants were similar between groups.

Table 3

Total isoflavone and genistein intake (milligrams per week) for mothers and Kawasaki cases and controls stratified by ethnicity

Isoflavone intake ^a	Whites (n = 278)		Asians (n = 49)		Other (n = 47) ^b	
	Controls	Cases	Controls	Cases	Controls	Cases
Mothers						
During pregnancy	n = 149	n = 129	n = 18	n = 31	n = 26	n = 21
Total isoflavones	4.2 (0–40.8)	2.0 (0–31.4)	52.7 (16.3–85.3)	61.7 (33.5–159.4)	0 (0–10.4)	0.1 (0–7.3)
Genistein	2.2 (0–22.0)	1.0 (0–16)	26.9 (8.3–40.8)	31.0 (16.6–82.4)	0 (0–5.1)	0 (0–4.0)
While breast-feeding ^c	n = 126	n = 116	n = 17	n = 28	n = 15	n = 13
Total isoflavones	6.9 (0.1–46.0)	4.0 (0.1–31.5)	52.4 (16.3–56.7)	60.7 (40.1–176.4)	0.3 (0–12.9)	2.9 (0–11.4)
Genistein	3.7 (0–23.2)	1.7 (0–16.3)	26.5 (8.3–30.8)	30.4 (20.1–89.7)	0.1 (0–6.8)	1.1 (0–6.2)
Children						
	Whites (n = 274)		Asians (n = 51)		Other (n = 49) ^b	
	Controls	Cases	Controls	Cases	Controls	Cases
Children	n = 148	n = 126	n = 21	n = 30	n = 24	n = 25
Total isoflavones	0 (0–8.6)	0 (0–13.4)	0 (0–25.4)	27.6 (2.9–59.6)	0 (0–0)	0 (0–29.3)
Genistein	0 (0–4.2)	0 (0–6.6)	0 (0–13.0)	13.7 (1.6–26.7)	0 (0–0)	0 (0–12.8)

Values expressed as median (interquartile range).

^aTotal isoflavones = sum of genistein, daidzein, and glycitein.

^b“Other ethnicity” includes 22 mixed races, 10 African Americans, 3 Native Americans, 1 Pacific Islander, and 11 not indicated (13 for children).

^cNot all mothers breastfed.

Table 4

Association between children's isoflavone intake (milligrams per week) and KD using soy nonconsumers as a reference, stratified by ethnicity

Isoflavone intake/categories ^a	Whites (n = 274)		Asians (n = 51)			
	IQR	No. of cases/controls	ORs (95% CI)	IQR	No. of cases/controls	ORs (95% CI)
Total isoflavones						
Soy nonconsumers, 0		75/91	1.00 (reference)		7/12	1.00 (reference)
Low consumers, 16.6	3.3–11.9	21/31	0.88 (0.46–1.70)	4.2–8.3	3/2	4.09 (0.46–36.18)
High consumers, >16.6	25.9–75.8	30/26	1.61 (0.86–3.01)	25.4–152.1	20/7	7.29 (1.73–30.75)
<i>P</i> trend			0.21			0.007
Continuous, mg/wk ^b		126/148	1.12 (0.97–1.30)		30/21	1.55 (1.11–2.17)
Genistein						
Soy nonconsumers, 0		75/91	1.00 (reference)		7/12	1.00 (reference)
Low consumers, 6.5	1.6–4.9	19/30	0.83 (0.42–1.62)	1.6–6.2	3/3	2.82 (0.38–21.12)
High consumers, >6.5	13.0–39.1	32/27	1.65 (0.89–3.05)	13.0–77.7	20/6	8.33 (1.92–36.24)
<i>P</i> trend			0.17			0.005
Continuous, mg/wk ^b		126/148	1.16 (0.97–1.39)		30/21	1.61 (1.10–2.37)

All analyses performed on log-transformed values, adjusted for age and sex; soy nonconsumers, reference.

Abbreviation: IQR, interquartile range for corresponding category.

^aSoy nonconsumers, reference group; low consumers, total isoflavone intakes below the median; high consumers, total isoflavone intakes above the median represent total intakes above and below the median among soy consumers, respectively.

^bBecause of small numbers of observations in some cells, an overall continuous model was also performed; continuous model includes soy nonconsumers.