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Original Research

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.

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

Abbreviations: CI, confidence interval; FFQ, food frequency questionnaire; KD, Kawasaki disease; OR, odds ratio; SCH, Seattle Children's Hospital.

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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 3 months. 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 breastfeeding 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 Vegenaise"; "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