

Soy, isoflavones, and prevalence of allergic rhinitis in Japanese women: The Osaka Maternal and Child Health Study

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Background: It has been hypothesized that isoflavones reduce the risk of many chronic diseases, but there are no data on the effects of dietary soy and isoflavone consumption on allergic disorders.

Objective: This cross-sectional study examined the relationship between dietary soy products and isoflavone intake and the prevalence of allergic rhinitis.

Methods: Study subjects were 1002 Japanese pregnant women. Allergic rhinitis (including cedar pollinosis) was defined as present if subjects had received drug treatment at some point during the previous 12 months. Adjustment was made for age; gestation; parity; cigarette smoking; passive smoking at home and at work; indoor domestic pets; family history of asthma, atopic eczema, and allergic rhinitis; family income; education; mite allergen level in house dust; changes in diet in the previous month; season when data were collected; and body mass index.

Results: Compared with dietary intake of total soy product, soy protein, daidzein, and genistein in the first quartile, consumption of these substances in the fourth quartile was independently associated with a reduced prevalence of allergic rhinitis, although no significant dose-response relationships were observed. A clear inverse linear trend for miso intake across quartiles was found, whereas the adjusted odds ratio for comparison of the highest with the lowest quartile was not statistically significant. Consumption of tofu, tofu products,

fermented soybeans, boiled soybeans, and miso soup was not related to the prevalence of allergic rhinitis.

Conclusion: A high intake of soy and isoflavones may be associated with a reduced prevalence of allergic rhinitis. (*J Allergy Clin Immunol* 2005;115:1176-83.)

Key words: Allergic rhinitis, cross-sectional study, isoflavones, Japanese women, soy

Phytoestrogens are secondary plant components structurally analogous to human estrogens and can bind estrogen receptors α and β .^{1,2} Phytoestrogens can be divided into 3 main classes: coumestans, lignans, and isoflavones. Isoflavones are thought to exert several biological effects, and it has been hypothesized that they reduce the risk of many chronic diseases.³ Daidzein and genistein are the main compounds within isoflavones and are found in high concentrations in soybeans. Possible preventive mechanisms in relation to soy or isoflavone intake include estrogenic or antiestrogenic activities, inhibition of several enzymes involved in signal transduction such as tyrosine protein kinases, inhibition of angiogenesis and atherosclerosis, and antioxidant properties.¹⁻⁵ Epidemiologic evidence regarding the association of soy or isoflavone consumption with breast cancer risk is limited. Results have been equivocal, although a recent cohort study in Japan showed that frequent miso soup and isoflavone intake was related to a decreased risk of breast cancer.⁶ Another prospective study in Japan found a marginally significant inverse relationship between soy product intake and total mortality.⁷

To our knowledge, no epidemiologic study has assessed the association between dietary soy or isoflavone consumption and allergic disorders. Estrogens have been shown to stimulate the immune system.^{8,9} Thus, dietary isoflavone intake may be likely to affect the host's immune system. Postmenopausal women showed significantly higher IL-6 values after a high-isoflavone soy diet compared with control values, whereas no significant effects were seen in TNF- α .¹⁰ Philpott et al¹¹ demonstrated nasal congestion in conjunction with the rise in serum estrogens that occurs at ovulation in the normal menstrual cycle, although the number of study subjects

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Abbreviations used

OMCHS: Osaka Maternal and Child Health Study
OR: Odds ratio

was small. Pharmacological antagonism of estrogens may relieve nasal congestion.

Japanese people consume quantities of soy that are likely to be physiologically meaningful. Therefore, we examined the relationship between dietary soy products and isoflavone intake and the prevalence of allergic rhinitis in Japanese pregnant women by using baseline data from the Osaka Maternal and Child Health Study (OMCHS).

METHODS

Study population

The OMCHS, an ongoing prospective cohort study, investigates preventive and risk factors for maternal and child health problems such as allergic disorders and postpartum depression. The OMCHS requested that pregnant women complete a baseline survey, which was followed by several postnatal surveys. In Japan, when women become pregnant, they notify the municipality of the domicile of the conception, and the municipality provides them with a maternal and child health handbook. Eligible subjects were those women who became pregnant in Neyagawa City, which is one of the 44 municipalities in Osaka Prefecture, a metropolis in Japan with a total population of approximately 8.8 million. During the period from November 2001 to March 2003, the Neyagawa City Government provided all pregnant women with a set of leaflets explaining our study, an application form, and a self-addressed and stamped return envelope together with the maternal and child health handbook. Research technicians asked all of the eligible women to take part in this study by telephone, excluding pregnant women who had already returned the application form to the data management center. Of the 3639 eligible subjects in Neyagawa City, 627 pregnant women (17.2%) participated in this study. Eight pregnant women who did not live in Neyagawa City but who had become aware of the current study at an obstetric clinic before August 2002 decided by themselves to participate in this study. Also, there were 77 participants who received explanations of the OMCHS from public health nurses in 6 other municipalities from August 2002 to March 2003. From October 2002 to March 2003, 290 participants were recruited from a university hospital and 3 obstetric hospitals in 3 other municipalities; these women were recommended for participation in the OMCHS by an obstetrician. Finally, a total of 1002 pregnant women gave their fully informed consent in writing and completed the baseline survey. The OMCHS was approved by the ethics committees of the Osaka City University School of Medicine and the Osaka Prefectural Institute of Public Health.

Measurements

In the baseline survey, each participant filled out a set of 2 self-administered questionnaires and collected 2 dust samples from a 1-m² area of the bedclothes and flooring for 1 minute by using a vacuum cleaner fitted with a collection apparatus. Participants then mailed these materials to the data management center. Research technicians completed missing or illogical data by telephone interview.

A validated self-administered diet history questionnaire was used to assess dietary habits over a period of 1 month. The structure and validity of the questionnaire were described in detail elsewhere.^{12,13}

In this instrument, intake of 147 food items was calculated by using an ad hoc computer algorithm developed to analyze the questionnaire. The questionnaire included 6 food items for soy products (tofu, tofu products such as deep-fried tofu and fried bean curd, fermented soybeans, boiled soybeans, miso, and miso soup). Total soy product intake was considered as the sum of these 6 food items. Soy protein intake was also calculated as the sum of the protein included in these food items. Isoflavone intake from soy products was estimated on the basis of previously published data on isoflavone concentrations in these soy foods summarized by Kimira et al.¹⁴ Energy-adjusted intake by the residual method was used for the analyses.¹⁵

A second self-administered questionnaire inquired about age; gestation; parity; smoking habits; passive smoking exposure; personal history of allergic rhinitis; family history of asthma, atopic eczema, and allergic rhinitis; indoor domestic pets; family income; education; weight; height; and changes in diet in the previous 1 month. Allergic rhinitis (including Japanese cedar pollinosis) was defined as present when subjects had been treated with medications at some time in the previous 12 months. A family history of asthma, atopic eczema, and allergic rhinitis (including Japanese cedar pollinosis) was considered to be present if 1 or more parents or siblings of the study subject had manifested any of these allergic disorders. Body mass index was calculated by dividing self-reported body weight (kilograms) by the square of self-reported height (meters).

Antigen levels from extracts of fine dust fractions were measured by a double-antibody sandwich ELISA using a soluble antigen prepared from whole *Dermatophagoides farinae* mite bodies as a reference standard and were expressed as antigen equivalent in micrograms per square meter of surface area (Mitey Checker; Shinto Fine Co, Ltd, Osaka, Japan).^{16,17} Antigen levels were semiquantitatively classified with scores of – (<2 µg/m²), ± (5 µg/m²), + (10–15 µg/m²), and ++ (>35 µg/m²). In the current study, we used only antigen levels in the sample collected from the bedclothes because the correlation between antigen levels from the bedclothes and flooring was almost collinear (Spearman correlation coefficient, 0.54; *P* < .0001).

Statistical analysis

Intake of selected foods and nutrients was categorized at quartile points on the basis of the distribution of all study subjects. Age was classified into 3 categories (<29, 29–31, and 32+ years), gestation into 3 (<15, 15–20, and 21+ weeks), parity into 2 (0 and 1+), cigarette smoking into 3 (never, former, and current), passive smoking at home into 3 (never, former, and current), passive smoking at work into 3 (never, former, and current), family income into 3 (Japanese yen <4,000,000, 4,000,000–5,999,999, and 6,000,000+/year), education into 3 (<13, 13–14, and 15+ years), dust mite allergen levels into 4 (–, ±, +, and ++), changes in diet in the previous 1 month into 3 (none or seldom, slight, and substantial), and season when data were collected into 4 (spring, summer, fall, and winter). Body mass index was used as a continuous variable.

Logistic regression analysis was used to compare the prevalence of allergic rhinitis with soy and isoflavone intake. Multiple logistic regression analysis was used to control for the potential confounding effects of selected factors. Trend of association was assessed by a logistic regression model assigning scores to the levels of the independent variable. Two-sided *P* values less than .05 were considered statistically significant. All computations were performed by using the SAS software package version 8.2 (SAS Institute, Inc, Cary, NC).

RESULTS

The prevalence value for allergic rhinitis (including Japanese cedar pollinosis) in the previous 12 months was

TABLE I. Distribution of selected characteristics in 1002 pregnant females, OMCHS, Japan

Variable	n (%) or Mean (SD)
Age (% y)	
<29	380 (37.9)
29-31	299 (29.8)
32+	323 (32.2)
Gestation (% wk)	
<15	357 (35.6)
15-20	329 (32.8)
21+	316 (31.5)
Parity of 1 or more (%)	513 (51.2)
Cigarette smoking (%)	
Never	697 (69.6)
Former	121 (12.1)
Current	184 (18.4)
Passive smoking at home (%)	
Never	284 (28.3)
Former	224 (22.4)
Current	494 (49.3)
Passive smoking at work (%)	
Never	344 (34.3)
Former	538 (53.7)
Current	120 (12.0)
Family history of asthma (%)	101 (10.1)
Family history of atopic eczema (%)	138 (13.8)
Family history of allergic rhinitis (%)	429 (42.8)
Indoor domestic pets (cats, dogs, birds, or hamsters; %)	114 (11.4)
Family income (% Japanese yen/y)	
<4,000,000	301 (30.0)
4,000,000-5,999,999	403 (40.2)
6,000,000+	298 (29.7)
Education (% y)	
<13	323 (32.2)
13-14	413 (41.2)
15+	266 (26.6)
Mite allergen level in house dust (%)*	
—	436 (43.5)
±	297 (29.6)
+	196 (19.6)
++	73 (7.3)
Body mass index (kg/m ²)	21.4 (2.8)
Changes in diet in the previous 1 month (%)	
None or seldom	300 (29.9)
Slight	435 (43.4)
Substantial	267 (26.7)
Season when data were collected (%)	
Spring	318 (31.7)
Summer	162 (16.2)
Fall	223 (22.3)
Winter	299 (29.8)

*Antigen levels were semiquantitatively classified with scores of — (<2 µg/m²), ± (5 µg/m²), + (10-15 µg/m²), and ++ (>35 µg/m²).

14.1% among 1002 pregnant women. The mean age was 29.8 years, and 30% of subjects were from 29 to 31 years old (Table I). About 70% of the women were enrolled by the 20th week of gestation, and about half had a parity of 1 or more. Many more participants had a family history of allergic rhinitis than a family history of asthma or atopic eczema. Slight or substantial changes in diet in

TABLE II. Distribution of daily soy and isoflavone intake in 1002 pregnant females, OMCHS, Japan*

Variable	Mean (SD)
Total energy, kJ	6815.3 (1793.7)
Total soy product, g	47.8 (27.8)
Tofu, g	6.3 (2.4)
Tofu products, g	24.2 (18.5)
Fermented soybeans, g	6.5 (7.4)
Boiled soybeans, g	6.9 (10.0)
Miso, g	2.6 (4.5)
Miso soup, g	1.3 (3.9)
Soy protein, g	4.5 (3.0)
Daidzein, mg	9.0 (6.1)
Genistein, mg	15.0 (10.1)

*Nutrient and food intake were adjusted for total energy intake by using the residual method.

the previous 1 month were experienced by 702 pregnant women because of nausea gravidarum (585 women), maternal and fetal health (107 women), and other reasons (10 women). Mean daily total energy and energy-adjusted total soy product consumption were 6815 kJ and 47.8 g, respectively (Table II). Total soy product intake was virtually unrelated to body mass index.

Odds ratios (ORs) and their 95% CIs for relationships between soy product intake and the prevalence of allergic rhinitis are presented in Table III. A significant inverse dose-response relationship between total soy product consumption and the prevalence of allergic rhinitis was observed (P for trend = .02). After adjustment for age, gestation, parity, cigarette smoking, passive smoking at home and at work, indoor domestic pets, family history of asthma, atopic eczema, and allergic rhinitis, family income, education, mite allergen level in house dust, changes in diet in the past 1 month, the season when data were collected, and body mass index, the inverse linear trend fell just short of the significance level, although the multivariate OR for comparison of the highest with the lowest quartile was 0.54 (95% CI, 0.30-0.97). We also found a clear inverse dose-response association for miso consumption. The inverse linear trend was slightly pronounced after adjustment for the confounders under study, although the multivariate OR for comparison of the highest with the lowest quartile was not statistically significant. Dietary intake of tofu, tofu products, fermented soybeans, boiled soybeans, and miso soup was not significantly associated with the prevalence of allergic rhinitis.

For dietary intake of soy protein, daidzein, and genistein, the multivariate ORs for comparison of the fourth with the first quartile were 0.55 (95% CI, 0.31-0.96), 0.52 (95% CI, 0.29-0.91), and 0.56 (95% CI, 0.31-0.97), respectively (Table IV). No inverse dose-response association between intake of soy protein, daidzein, or genistein and the prevalence of allergic rhinitis was statistically significant in the multivariate model, however.

After further adjustment for daidzein or genistein intake, a statistically significant inverse association

TABLE III. ORs and 95% CIs for allergic rhinitis by quartiles of soy product intake, OMCHS, Japan

Variable*	Prevalence	Crude OR (95% CI)	Adjusted OR (95% CI)†
Total soy product			
Q1 (21.5)	41/250 (16.4%)	1.00	1.00
Q2 (34.9)	39/251 (15.5%)	0.94 (0.58-1.51)	0.98 (0.58-1.63)
Q3 (49.7)	39/250 (15.6%)	0.94 (0.58-1.52)	0.95 (0.57-1.59)
Q4 (82.7)	22/251 (8.8%)	0.49 (0.28-0.84)	0.54 (0.30-0.97)
<i>P</i> for trend		.02	.06
Tofu			
Q1 (3.8)	37/250 (14.8%)	1.00	1.00
Q2 (5.4)	34/251 (13.6%)	0.90 (0.54-1.49)	0.97 (0.57-1.65)
Q3 (6.8)	31/250 (12.4%)	0.82 (0.49-1.36)	0.87 (0.50-1.49)
Q4 (8.8)	39/251 (15.5%)	1.06 (0.65-1.73)	1.21 (0.72-2.05)
<i>P</i> for trend		.91	.59
Tofu products			
Q1 (7.0)	39/250 (15.6%)	1.00	1.00
Q2 (14.0)	40/251 (15.9%)	1.03 (0.63-1.66)	1.08 (0.65-1.81)
Q3 (26.0)	34/250 (13.6%)	0.85 (0.52-1.40)	0.83 (0.48-1.41)
Q4 (48.7)	28/251 (11.2%)	0.68 (0.40-1.14)	0.75 (0.43-1.31)
<i>P</i> for trend		.11	.21
Fermented soybeans			
Q1 (1.0)	37/250 (14.8%)	1.00	1.00
Q2 (3.6)	43/251 (17.1%)	1.19 (0.74-1.93)	1.15 (0.69-1.93)
Q3 (5.9)	24/250 (9.6%)	0.61 (0.35-1.05)	0.64 (0.35-1.13)
Q4 (14.6)	37/251 (14.7%)	1.00 (0.61-1.63)	1.11 (0.65-1.88)
<i>P</i> for trend		.43	.76
Boiled soybeans			
Q1 (−0.4)	43/250 (17.2%)	1.00	1.00
Q2 (2.1)	32/251 (12.8%)	0.70 (0.43-1.15)	0.66 (0.38-1.12)
Q3 (5.5)	31/250 (12.4%)	0.68 (0.41-1.12)	0.65 (0.38-1.10)
Q4 (15.3)	35/251 (13.9%)	0.78 (0.48-1.27)	0.75 (0.45-1.26)
<i>P</i> for trend		.30	.29
Miso			
Q1 (−0.2)	39/250 (15.6%)	1.00	1.00
Q2 (0.9)	44/251 (17.5%)	1.15 (0.72-1.85)	1.17 (0.71-1.93)
Q3 (2.3)	31/250 (12.4%)	0.77 (0.46-1.27)	0.63 (0.37-1.09)
Q4 (5.3)	27/251 (10.8%)	0.65 (0.38-1.10)	0.59 (0.33-1.03)
<i>P</i> for trend		.05	.02
Miso soup			
Q1 (−0.4)	42/250 (16.8%)	1.00	1.00
Q2 (0.1)	31/251 (12.4%)	0.70 (0.42-1.15)	0.68 (0.39-1.16)
Q3 (0.4)	31/250 (12.4%)	0.70 (0.42-1.15)	0.70 (0.41-1.18)
Q4 (3.5)	37/251 (14.7%)	0.86 (0.53-1.39)	0.91 (0.54-1.54)
<i>P</i> for trend		.53	.73

*Quartile medians in g/d adjusted energy intake using the residual method are given in parentheses.

†Adjustment for age; gestation; parity; cigarette smoking; passive smoking at home and at work; indoor domestic pets; family history of asthma, atopic eczema, and allergic rhinitis; family income; education; mite allergen level in house dust; changes in diet in the previous 1 month; season when data were collected; and body mass index (continuous).

between total soy product consumption and the prevalence of allergic rhinitis had completely disappeared.

Total soy product intake was highly correlated with consumption of green and yellow and other vegetables, seaweed, fish, meat, eggs, and dairy products (Table V). Our previous findings showed that dietary intake of seaweed was significantly associated with a decreased prevalence of allergic rhinitis (Miyake et al, submitted for publication October 2004). There was no statistically significant relationship of intake of green and yellow and other vegetables, fish, meat, eggs, and dairy products with allergic rhinitis. Additional adjustment for

green and yellow vegetables, other vegetables, meat, or egg intake did not materially alter the significant inverse association between total soy product consumption in the highest quartile and the prevalence of allergic rhinitis. After further control for seaweed or fish intake, the inverse association of total soy product intake with allergic rhinitis was not statistically significant (adjusted ORs for comparison of the highest with the lowest quartile, 0.64 [95% CI, 0.34-1.17] and 0.59 [95% CI, 0.32-1.06], respectively) whereas intake of seaweed but not fish was independently related to a decreased prevalence of allergic rhinitis.

TABLE IV. ORs and 95% CIs for allergic rhinitis by quartiles of soy protein and isoflavone intake, OMCHS, Japan

Variable*	Prevalence	Crude OR (95% CI)	Adjusted OR (95% CI)†
Soy protein			
Q1 (1.8)	42/250 (16.8%)	1.00	1.00
Q2 (3.2)	34/251 (13.6%)	0.78 (0.47-1.27)	0.75 (0.45-1.27)
Q3 (4.7)	42/250 (16.8%)	1.00 (0.63-1.60)	1.10 (0.66-1.82)
Q4 (7.8)	23/251 (9.2%)	0.50 (0.29-0.85)	0.55 (0.31-0.96)
<i>P</i> for trend		.05	.15
Daidzein			
Q1 (3.3)	42/250 (16.8%)	1.00	1.00
Q2 (6.3)	34/251 (13.6%)	0.78 (0.47-1.27)	0.71 (0.42-1.19)
Q3 (9.3)	42/250 (16.8%)	1.00 (0.63-1.60)	1.05 (0.64-1.74)
Q4 (15.3)	23/251 (9.2%)	0.50 (0.29-0.85)	0.52 (0.29-0.91)
<i>P</i> for trend		.05	.11
Genistein			
Q1 (5.6)	42/250 (16.8%)	1.00	1.00
Q2 (10.6)	33/251 (13.2%)	0.75 (0.46-1.23)	0.69 (0.40-1.16)
Q3 (15.4)	42/250 (16.8%)	1.00 (0.63-1.60)	1.02 (0.62-1.69)
Q4 (26.0)	24/251 (9.6%)	0.52 (0.30-0.89)	0.56 (0.31-0.97)
<i>P</i> for trend		.07	.15

*Quartile medians in mg/d (except for soy protein, g/d) adjusted energy intake using the residual method are given in parentheses.

†Adjustment for age; gestation; parity; cigarette smoking; passive smoking at home and at work; indoor domestic pets; family history of asthma, atopic eczema, and allergic rhinitis; family income; education; mite allergen level in house dust; changes in diet in the previous 1 month; season when data were collected; and body mass index (continuous).

TABLE V. Spearman rank correlation coefficients (*P* values) of total soy product intake with consumption of selected dietary variables, OMCHS, Japan

Dietary variable*	Spearman rank correlation coefficient (<i>P</i> value)
Fruit	−0.05 (.10)
Green and yellow vegetables	0.36 (<.0001)
Other vegetables	0.26 (<.0001)
Seaweed	0.37 (<.0001)
Fish	0.24 (<.0001)
Meat	0.12 (<.0001)
Eggs	0.12 (.0002)
Dairy products	0.01 (.77)

*Total energy-adjusted dietary variable using the residual method was categorized at quartile points.

DISCUSSION

The current cross-sectional study found that compared with dietary intake of total soy product, soy protein, daidzein, and genistein in the first quartile, consumption of these substances in the fourth quartile was independently associated with a reduced prevalence of allergic rhinitis, although significant dose-response relationships between their intake and the prevalence of allergic rhinitis were not observed. A clear inverse linear trend for miso intake across quartiles was found, whereas the multivariate OR for comparison of the highest with the lowest quartile was not statistically significant. Consumption of tofu, tofu products, fermented soybeans, boiled soybeans, and miso soup was not significantly related to the prevalence of allergic rhinitis. These data are likely to support the

hypothesis that a high intake of soy is associated with a reduced prevalence of allergic rhinitis.

Several previous studies assessed the relationships between fatty acids and foods high in fatty acids¹⁸⁻²⁸ and fruit and antioxidants^{27,28} and allergic rhinitis; the results were inconsistent. As far as we know, this is the first analytic epidemiological study on the association between soy and isoflavone intake and allergic rhinitis using a validated questionnaire with a broad range of categories for soy products. In Japan, the prevalence of allergic rhinitis is the highest among all allergic disorders, and the prevalence value for allergic rhinoconjunctivitis was 24% in Japanese adolescents in Osaka on the basis of diagnostic criteria in the International Study of Asthma and Allergies in Childhood.²⁹⁻³¹ This figure is generally higher than in adolescents in Western countries.³² The Study of Women's Health Across the Nation demonstrated that median intakes of daidzein and genistein by white subjects, African American subjects, and Japanese subjects in the United States were 6.2 $\mu\text{g/d}$ and 3.9 $\mu\text{g/d}$, 2.7 $\mu\text{g/d}$ and 1.7 $\mu\text{g/d}$, and 4676 $\mu\text{g/d}$ and 7151 $\mu\text{g/d}$, respectively.³³ The corresponding figures for the current study were 7264 $\mu\text{g/d}$ and 12,029 $\mu\text{g/d}$, respectively. Our findings point to a paradox in the prevalence of allergic rhinitis between Japan and Western countries that cannot be explained by dietary intake of soy and isoflavones. Thus, the difference in prevalence is likely to be a result of other environmental or genetic factors. In particular, high exposure to cedar pollen is likely to be ubiquitous in the entire country in Japan. Automobile exhaust is also suggested.²⁹

We have no immediate explanation for the inverse association of total soy product, miso, soy protein, and

isoflavone intake with the prevalence of allergic rhinitis. Because the potential protective effects of total soy product intake on allergic rhinitis essentially disappeared when we additionally adjusted for daidzein or genistein intake, isoflavone consumption might explain the association with total soy product. A laboratory study demonstrated that daidzein or genistein treatments significantly decreased IL-6 production in a dose-dependent manner in 2 human fetal osteoblastic cell lines.³⁴ It is also possible that soy protein might be an etiologically important agent. We could not find an investigation on the association between soy protein intake and the immune system. However, 1 study showed that soy protein isolate depleted of isoflavones, as well as purified isoflavones, was an effective inhibitor of 7,12-dimethylbenzanthracene-induced mammary tumors in adult rats.³⁵ Alternatively, uncontrolled dietary or nondietary factors may have confounded the relationship between total soy product and isoflavone intake and the prevalence of allergic rhinitis. Japanese persons who have a quite high intake of soy products are likely to follow traditional Japanese diet or behaviors that may be preventive against allergic disorders. An inverse relationship between total soy product intake and allergic rhinitis was attenuated by adjusting further for seaweed or fish consumption in the current study. Thus, the observed inverse relationship might to some extent be attributed to intake of seaweed or fish or unknown factors in relation to these foods.

The current study had several methodological advantages: the homogeneity of study subjects with respect to all being pregnant and adjustment for extensive information on potential confounding factors. We were not able to control for external factors such as aeroallergens and air pollution, however. The estimations of isoflavone intake as well as soy consumption were derived from a self-administered semiquantitative dietary assessment questionnaire. Because the dietary habits of the subjects were not actually observed, we could only approximate consumption. However, patients with allergic rhinitis might not be aware of the ill effects of diet. The consequence would have been an underestimation of values in our results because of a nondifferential exposure misclassification. Our diet history questionnaire was designed to assess recent dietary intake, ie, for 1 month before completing the questionnaire. Allowance for season when data were collected is likely to alleviate this weakness, however. Changes in diet in the past 1 month were controlled for because pregnant women are likely to change their diet for reasons such as nausea gravidarum. There are other limitations that should be considered. Of a total of 3639 eligible pregnant women in Neyagawa City, only 627 (17.2%) participated in this study. We were not able to assess a difference between participants and nonparticipants in Neyagawa City, because information on personal characteristics such as age, socioeconomic status, and a history of allergic disorders among the nonparticipants was not available. With regard to the remaining 375 participants, we were not able to calculate the participation rate because the exact number of eligible

subjects was not available. Also, we could not compare participants with nonparticipants in the 4 collaborating hospitals and 6 municipalities. Our subjects were an unrepresentative sample of Japanese women in the general population, and the current findings may not be generalized. In fact, educational levels were higher in the current study population than in the general population. According to the 2000 population census of Japan, the proportions of women age 30 to 34 years in Osaka Prefecture with years of education of <13, 13 to 14, 15+, and unknown were 49.2%, 32.3%, 13.6%, and 4.9%, respectively.³⁶ The corresponding figures for the current study were 32.2%, 41.2%, 26.6%, and 0.0%, respectively. It is difficult to know whether our study subjects represented a different group regarding the exposures, outcome, or confounders under investigation. We are uncertain whether the inverse association of soy and isoflavone intake with allergic rhinitis could also be found in Japanese men. In a cross-sectional study in German adults, most statistically significant effects in relation to fat consumption and allergic disease were limited to women, and the differences might be partly ascribed to sex-specific dietary patterns.¹⁹ Japanese cedar pollinosis is a seasonal disorder with a high prevalence that is often undiagnosed.³⁷ We did not use validated diagnostic criteria for allergic rhinitis such as those reported in the International Study of Asthma and Allergies in Childhood. Also, we were not able to distinguish perennial from seasonal forms of allergic rhinitis. Because the definition of allergic rhinitis was based on drug treatment, there was a loss of patients with milder disease. Moreover, women who want to become pregnant or are pregnant might tend to avoid drugs. The median and the 95th percentile values of total serum IgE concentrations were 123 IU/mL and 761 IU/mL, respectively, in 139 cases, and 68 IU/mL and 734 IU/mL, respectively, in 842 noncases, although data on specific IgE were not available in this study. The magnitude of misclassification of the outcome was unlikely to be different among all 4 categories of dietary factors under investigation. The consequence would bias the estimates of the association toward the null.

The interface between allergy/immunology and pregnancy should be discussed, which may have an influence on the association of interest. It has been suggested that pregnancy involves a shift to the T_H2 side of the immune response,³⁸ although Chaouat et al³⁹ pointed out the importance of the role of natural killer and IL-12, IL-15, and IL-18 tripods in successful or failed pregnancy in human beings beyond the T_H1/T_H2 paradigm. The hormonal changes in pregnancy are often invoked to explain an apparent association between rhinitis symptoms and pregnancy. However, rhinitis ascribed solely to pregnancy may not be a distinct entity because most pregnant women do not have significant nasal symptoms.³⁸ In the current study, 105 of 141 current patients with allergic rhinitis (74.5%) had been treated with medications at some time for 1 or more years.

The findings from the current cross-sectional study do not necessarily indicate a causal relationship between soy

and isoflavone intake and allergic rhinitis. Soy is among the potent food allergens. Further investigations are needed to answer the question of whether soy and isoflavone consumption is independently preventive against allergic rhinitis, taking into consideration additional environmental factors as well as genetic factors. Research regarding biological mechanisms is also particularly required.

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REFERENCES

- Bingham SA, Atkinson C, Liggins J, Bluck L, Coward A. Phytoestrogens: where are we now? *Br J Nutr* 1998;79:393-406.
- Nikov GN, Hopkins NE, Boue S, Alworth WL. Interactions of dietary estrogens with human estrogen receptors and the effect on estrogen receptor-estrogen response element complex formation. *Environ Health Perspect* 2000;108:867-72.
- Messina MJ. Legumes and soybeans: overview of their nutritional profiles and health effects. *Am J Clin Nutr* 1999;70(suppl 3):439S-50S.
- Fotsis T, Pepper M, Adlercreutz H, Hase T, Montesano R, Schweigerer L. Genistein, a dietary ingested isoflavonoid, inhibits cell proliferation and in vitro angiogenesis. *J Nutr* 1995;125(suppl 3):790S-7S.
- Anthony MS, Clarkson TB, Williams JK. Effects of soy isoflavones on atherosclerosis: potential mechanisms. *Am J Clin Nutr* 1998;68(suppl 6):1390S-3S.
- Yamamoto S, Sobue T, Kobayashi M, Sasaki S, Tsugane S, Japan Public Health Center-Based Prospective Study on Cancer Cardiovascular Diseases Group. Soy, isoflavones, and breast cancer risk in Japan. *J Natl Cancer Inst* 2003;95:906-13.
- Nagata C, Takatsuka N, Shimizu H. Soy and fish oil intake and mortality in a Japanese community. *Am J Epidemiol* 2002;156:824-31.
- Li ZG, Danis VA, Brooks PM. Effect of gonadal steroids on the production of IL-1 and IL-6 by blood mononuclear cells in vitro. *Clin Exp Rheumatol* 1993;11:157-62.
- Knoferl MW, Jarrar D, Angele MK, Ayala A, Schwacha MG, Bland KI, et al. 17 beta-Estradiol normalizes immune responses in ovariectomized females after trauma-hemorrhage. *Am J Physiol Cell Physiol* 2001;281:C1131-8.
- Jenkins DJA, Kendall CWC, Connelly PW, Jackson CJC, Parker T, Faulkner D, et al. Effects of high- and low-isoflavone (phytoestrogen) soy foods on inflammatory biomarkers and proinflammatory cytokines in middle-aged men and women. *Metabolism* 2002;51:919-24.
- Philpott CM, El-Alami M, Murty GE. The effect of the steroid sex hormones on the nasal airway during the normal menstrual cycle. *Clin Otolaryngol* 2004;29:138-42.
- Sasaki S, Yanagibori R, Amano K. Self-administered diet history questionnaire developed for health education: a relative validation of the test-version by comparison with 3-day diet record in women. *J Epidemiol* 1998;8:203-15.
- Sasaki S, Ushio F, Amano K, Morihara M, Todoriki T, Uehara Y, et al. Serum biomarker-based validation of a self-administered diet history questionnaire for Japanese subjects. *J Nutr Sci Vitaminol* 2000;46:285-96.
- Kimura M, Arai Y, Shimoi K, Watanabe S. Japanese intake of flavonoids and isoflavonoids from foods. *J Epidemiol* 1998;8:168-75.
- Willett W, Stampfer MJ. Total energy intake: implications for epidemiologic analyses. *Am J Epidemiol* 1986;124:17-27.
- Konishi E, Uehara K. Antigen levels of Dermatophagoides mites (Acari: Pyroglyphidae) in dust samples collected in homes of allergic patients. *J Med Entomol* 1994;31:394-9.
- Takai T, Yuuki T, Okumura Y, Mori A, Okudaira H. Determination of the N- and C-terminal sequences required to bind human IgE of the major house dust mite allergen Der f 2 and epitope mapping for monoclonal antibodies. *Mol Immunol* 1997;34:255-61.
- von Mutius E, Weiland SK, Fritzsche C, Duhme H, Keil U. Increasing prevalence of hay fever and atopy among children in Leipzig, East Germany. *Lancet* 1998;351:862-6.
- Trak-Fellermeier MA, Brasche S, Winkler G, Koletzko B, Heinrich J. Food and fatty acid intake and atopic disease in adults. *Eur Respir J* 2004;23:575-82.
- Nafstad P, Nystad W, Magnus P, Jaakkola JJK. Asthma and allergic rhinitis at 4 years of age in relation to fish consumption in infancy. *J Asthma* 2003;40:343-8.
- Farchi S, Forastiere F, Agabiti N, Corbo G, Pistelli R, Fortes C, et al. Dietary factors associated with wheezing and allergic rhinitis in children. *Eur Respir J* 2003;22:772-80.
- Huang SL, Lin KC, Pan WH. Dietary factors associated with physician-diagnosed asthma and allergic rhinitis in teenagers: analyses of the first Nutrition and Health Survey in Taiwan. *Clin Exp Allergy* 2001;31:259-64.
- Dunder T, Kuikka L, Turtinen J, Räsänen L, Uhari M. Diet, serum fatty acids, and atopic diseases in childhood. *Allergy* 2001;56:425-8.
- Bolte G, Frye C, Hoelscher B, Meyer I, Wjst M, Heinrich J. Margarine consumption and allergy in children. *Am J Respir Crit Care Med* 2001;163:277-9.
- Wickens K, Lane JM, Fitzharris P, Siebers R, Riley G, Douwes J, et al. Farm residence and exposures and the risk of allergic diseases in New Zealand children. *Allergy* 2002;57:1171-9.
- Wakai K, Okamoto K, Tamakoshi A, Lin Y, Nakayama T, Ohno Y. Seasonal allergic rhinoconjunctivitis and fatty acid intake: a cross-sectional study in Japan. *Ann Epidemiol* 2001;11:59-64.
- Nagel G, Nieters A, Becker N, Linseisen J. The influence of the dietary intake of fatty acids and antioxidants on hay fever in adults. *Allergy* 2003;58:1277-84.
- Huang SL, Pan WH. Dietary fats and asthma in teenagers: analyses of the first Nutrition and Health Survey in Taiwan (NAHSIT). *Clin Exp Allergy* 2001;31:1875-80.
- Miyake Y, Yura A, Iki M. Relationship between distance from major roads and adolescent health in Japan. *J Epidemiol* 2002;12:418-23.
- Miyake Y, Yura A, Iki M. Breastfeeding and the prevalence of symptoms of allergic disorders in Japanese adolescents. *Clin Exp Allergy* 2003;33:312-6.
- Miyake Y, Yura A, Iki M. Cross-sectional study of allergic disorders in relation to familial factors in Japanese adolescents. *Acta Paediatr* 2004;93:380-5.
- Strachan D, Sibbald B, Weiland S, Ait-Khaled N, Anabwani G, Anderson HR, et al. Worldwide variations in prevalence of symptoms of allergic rhinoconjunctivitis in children: the International Study of Asthma and Allergies in Childhood (ISAAC). *Pediatr Allergy Immunol* 1997;8:161-76.
- Greendale GA, FitzGerald G, Huang MH, Sternfeld B, Gold E, Seeman T, et al. Dietary soy isoflavones and bone mineral density: results from the study of women's health across the nation. *Am J Epidemiol* 2002;155:746-54.
- Chen XW, Garner SC, Anderson JJ. Isoflavones regulate interleukin-6 and osteoprotegerin synthesis during osteoblast cell differentiation via an estrogen-receptor-dependent pathway. *Biochem Biophys Res Commun* 2002;295:417-22.
- Constantinou AI, Lantvit D, Hawthorne M, Xu X, van Breemen RB, Pezzuto JM. Chemopreventive effects of soy protein and purified soy isoflavones on DMBA-induced mammary tumors in female Sprague-Dawley rats. *Nutr Cancer* 2001;41:75-81.
- Statistic Bureau, Ministry of Public Management, Home Affairs, Posts and Telecommunications, Japan. 2000 population census of Japan, vol. 3-2-27, labour force status of population, industry (major groups) of employed persons, and education. Osaka-fu. Tokyo, Japan: Statistic Bureau, Ministry of Public Management, Home Affairs, Posts and Telecommunications, Japan; 2002.
- Okuda M. Epidemiology of Japanese cedar pollinosis throughout Japan. *Ann Allergy Asthma Immunol* 2003;91:288-96.
- Palmer GW, Claman HN. Pregnancy and immunology: selected aspects. *Ann Allergy Asthma Immunol* 2002;89:350-9.

39. Chaouat G, Ledée-Bataille N, Dubanchet S, Zourbas S, Sandra O, Martal J. TH1/TH2 paradigm in pregnancy: paradigm lost? cytokines in pregnancy/early abortion: reexamining the TH1/TH2 paradigm. *Int Arch Allergy Immunol* 2004;134:93-119.

APPENDIX

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