

# Association of active and passive smoking with allergic disorders in pregnant Japanese women: baseline data from the Osaka Maternal and Child Health Study

Yoshihiro Miyake, MD, PhD\*; Shoichi Miyamoto, MBA†; Yukihiro Ohya, MD, PhD‡; Satoshi Sasaki, MD, PhD§; Ichiro Matsunaga, ME¶; Toshiaki Yoshida, PhD¶; Yoshio Hirota, MD, PhD†; and Hajime Oda, MD, PhD¶; for the Osaka Maternal and Child Health Study Group

**Background:** Evidence remains inconclusive as to whether smoking is a risk factor for allergic disorders in adults.

**Objective:** To investigate the relationship between active and passive smoking exposure and allergic disorders in pregnant Japanese women.

**Methods:** This cross-sectional study included 1,002 pregnant women. Participants were classified as having asthma after the age of 18 years if they had used an asthma medication at any time after reaching the age of 18 years. Current atopic eczema and allergic rhinitis (including cedar pollinosis) were defined as being present if participants had received any drug treatment during the previous 12 months. Adjustment was made for age; gestation; parity; family history of asthma, atopic eczema, and allergic rhinitis; indoor domestic pets; family income; education; and the mite antigen level in house dust.

**Results:** Current smoking, but not environmental tobacco smoke exposure, was independently related to an increased prevalence of asthma after the age of 18 years (adjusted odds ratio [OR], 2.66; 95% confidence interval [CI], 1.30–5.38). A significant positive association of current passive smoking exposure at home (adjusted OR, 1.89; 95% CI, 1.10–3.30) and at work (adjusted OR, 2.50; 95% CI, 1.29–4.76) with the prevalence of current allergic rhinitis was observed, whereas no measurable association with active smoking exposure was found. Neither active nor passive smoking was statistically significantly related to the prevalence of current atopic eczema.

**Conclusions:** These findings suggest that active smoking and environmental tobacco smoke exposure may increase the likelihood of asthma and allergic rhinitis, respectively, in pregnant Japanese women.

*Ann Allergy Asthma Immunol.* 2005;94:644–651.

## INTRODUCTION

Although many epidemiologic studies<sup>1–16</sup> have investigated a possible association between exposure to tobacco smoke and allergic disorders, evidence remains inconclusive as to

whether smoking is a risk factor for allergic disorders, especially in adults. A prospective study<sup>1</sup> in Swedish adults showed that current and former smoking presented significant risk factors for self-reported asthma compared with nonsmok-

\* Department of Public Health, Fukuoka University School of Medicine, Fukuoka, Japan.

† Department of Public Health, Osaka City University School of Medicine, Osaka, Japan.

‡ Division of Allergy, Department of Medical Specialties, National Center for Child Health and Development, Tokyo, Japan.

§ Project of Scientific Evaluation of Dietary Reference Intakes, National Institute of Health and Nutrition, Tokyo, Japan.

¶ Osaka Prefectural Institute of Public Health, Osaka, Japan.

The other members of the Osaka Maternal and Child Health Study Group are as follows: Hideharu Kanzaki, MD, PhD, and Mitsuyoshi Kitada, MD, PhD (Department of Obstetrics and Gynecology, Kansai Medical University); Yorihiro Horikoshi, MD, PhD (Department of Obstetrics and Gynecology, Kansai Medical University Kori); Osamu Ishiko, MD, PhD, Yuichiro Nakai, MD, PhD, Junko Nishio, MD, PhD, and Seiichi Yamamasu, MD, PhD (Department of Obstetrics and Gynecology, Osaka City University Graduate School of Medicine); Jinsuke Yasuda, MD, PhD (Department of Obstetrics and Gynecology, Matsushita Memorial Hospital); Seigo Kawai, MD, PhD (Department of Obstetrics and Gynecology, Hoshigaoka Koseinenkin Hos-

pital); Kazumi Yanagihara, MD, PhD (Yanagihara Clinic); Koji Wakuda, MD, PhD (Department of Obstetrics and Gynecology, Fujimoto Hospital); Tokio Kawashima, MD, PhD (Kyohritsu Women's Clinic); Katsuhiko Narimoto, MD, PhD (Ishida Hospital Obstetrics, Gynecology); Yoshihiko Iwasa, MD, PhD (Iwasa Women's Clinic); Katsuhiko Orino, MD, PhD (Orino Lady's Clinic); Itsuo Tsunetoh, MD, PhD (Tsunetoh Obstetrics and Gynecology); Junichi Yoshida, MD, PhD (Yoshida Clinic); Junichi Iito, MD, PhD (Iito Obstetrics and Gynecology Clinic); Takuzi Kaneko, MD, PhD (Kaneko Sanfujinka); Takao Kamiya, MD, PhD (Kamiya Ladies Clinic); Hiroyuki Kuribayashi, MD, PhD (Kuribayashi Clinic); Takeshi Taniguchi, MD, PhD (Taniguchi Hospital); Hideo Takemura, MD, PhD (Kosaka Women's Hospital); and Yasuhiko Morimoto, MD, PhD (Aizenbashi Hospital).

This study was supported by a Grant-in-Aid (13770206) for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology and by Health and Labour Sciences Research Grants from the Ministry of Health, Labour, and Welfare, Japan.

Received for publication July 5, 2004.

Accepted for publication in revised form January 31, 2005.

ing. The National Population Health Survey in Canada demonstrated that the incidence of asthma was not related to smoking status in males and females 12 years and older, although a significant positive association between smoking and asthma was observed among females who had pets at home.<sup>2</sup> The Nurses' Health Study found that current smokers were at lower risk for asthma than women who had never smoked and that the risk of asthma in past smokers was initially elevated but decreased as the time since they quit smoking increased.<sup>3</sup> The healthy smoker effect may have concealed true increases in the risk of asthma in relation to smoking in that study, however. Few epidemiologic studies<sup>4-6,15,16</sup> have reported a relationship between smoking habits and atopic eczema and allergic rhinitis in adults.

On the other hand, limited epidemiologic studies<sup>5,6,17-21</sup> have examined the relationship between exposure to environmental tobacco smoke (ETS) and allergic disorders in adults. A cross-sectional study<sup>17</sup> in Swiss adults who had never smoked found that passive smoking exposure at home or at work was significantly associated with an increased prevalence of physician-diagnosed asthma, with evidence of a dose-dependent increase with hours per day of exposure. There was no measurable relationship between exposure to ETS and allergic rhinitis in cross-sectional studies in Switzerland<sup>17</sup> and Singapore<sup>6</sup> or in the European Community Respiratory Health Survey.<sup>21</sup>

In view of the scarcity of epidemiologic information regarding the relationship between exposure to smoking and allergic disorders in Japan, we analyzed baseline data from the Osaka Maternal and Child Health Study to investigate the effects of active and passive smoking on the prevalence of asthma, atopic eczema, and allergic rhinitis in pregnant Japanese women using a cross-sectional design. In pregnant women, a significant positive association between active, but not passive, smoking and total serum IgE levels was reported in a previous study,<sup>22</sup> whereas spousal smoking was significantly positively related to maternal total IgE levels in France.<sup>23</sup>

## METHODS

### *Study Population*

The Osaka Maternal and Child Health Study is an ongoing prospective cohort study that investigates preventive and risk factors for maternal and child health problems, such as allergic disorders and postpartum depression. The Osaka Maternal and Child Health Study consists of a baseline survey completed by pregnant women and several postnatal follow-up 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 women were those who became pregnant in Neyagawa City, which is 1 of the 44 municipalities in Osaka Prefecture, a metropolis in Japan with a total population of approximately 8.8 million. Between November 1, 2001, and March 31, 2003, all pregnant women received a set of leaflets explaining the study, an application form, and a self-addressed and stamped return envelop along with the

maternal and child health handbook from the Neyagawa City government. Research technicians asked all of the eligible women to participate in this study by telephone, excluding pregnant women who had already returned the application form to the data management center. Of the 3,639 eligible women, 627 (17.2%) in Neyagawa City took part in this study. Eight pregnant women who did not live in Neyagawa City but who had become aware of the study at an obstetric clinic before August 2002 decided by themselves to participate in this study. Also, there were 77 participants who received explanations regarding the Osaka Maternal and Child Health Study from public health nurses in 6 other municipalities between August 1, 2002, and March 31, 2003. Between October 1, 2002, and March 31, 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 Osaka Maternal and Child Health Study by an obstetrician. Finally, a total of 1,002 pregnant women gave their fully informed consent in writing and completed a baseline survey. The ethics committees of the Osaka City University School of Medicine and the Osaka Prefectural Institute of Public Health approved this study.

### *Measurements*

In the baseline survey, each participant filled out a set of 2 self-administered questionnaires, put a passive diffusion sampling tube on her clothes for 24 hours on a usual day to measure concentrations of nitrogen dioxide and formaldehyde, and collected 2 dust samples from a 1-m<sup>2</sup> area of the bedclothes and flooring for 1 minute 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.

One of the self-administered questionnaires elicited information on age; gestation; parity; indoor domestic pets; family income; education; personal history of asthma, atopic eczema, and allergic rhinitis; family history of asthma, atopic eczema, and allergic rhinitis; smoking habits; and passive smoking exposure. Current asthma, atopic eczema, and allergic rhinitis (including cedar pollinosis) were defined as being present if participants had been treated with medications at some time in the previous 12 months, although data on the types of medications and the duration of their use were not available. Participants were classified as having asthma after the age of 18 years if they had used an asthma medication at any time after reaching the age of 18 years. A family history of asthma, atopic eczema, and allergic rhinitis (including cedar pollinosis) was considered to be present if 1 or more parents or siblings of the study participant had manifested any of these allergic disorders.

Antigen levels from extracts of fine dust fractions were measured using a double-antibody sandwich enzyme-linked immunosorbent assay using a soluble antigen prepared from whole *Dermatophagoides farinae* mite bodies as a reference standard and were expressed as antigen equivalent in micro-

grams per square meter of surface area (Mitey checker; Shinto Fine Co Ltd, Osaka, Japan).<sup>24,25</sup> Antigen levels were semiquantitatively classified with scores of  $- (<2 \mu\text{g}/\text{m}^2)$ ,  $\pm (5 \mu\text{g}/\text{m}^2)$ ,  $+ (10\text{--}15 \mu\text{g}/\text{m}^2)$ , and  $++ (>35 \mu\text{g}/\text{m}^2)$ . In the present 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;  $P < .0001$ ). The other instrument was a validated self-administered diet history questionnaire. Data regarding diet and concentrations of formaldehyde and nitrogen dioxide were not used in this study.

#### Statistical Analysis

Multiple logistic regression analysis was used to estimate adjusted odds ratios (ORs) and their 95% confidence intervals (CIs) for allergic disorders relative to active and passive smoking exposure. The analysis of the effects of ETS exposure at home and at work on allergic disorders was based only on the 697 participants who had never smoked. Age; gestation; parity; family history of asthma, atopic eczema, and allergic rhinitis; indoor domestic pets; family income; education; and the mite antigen level in house dust were selected a priori as potential confounding factors. Cigarette smoking was classified into 3 categories (never, former, and current), pack-years of smoking into 3 categories (none, 0.1–4.9, and  $\geq 5.0$ ), passive smoking at home into 3 categories (never, former, and current), pack-years of passive smoking at home into 3 categories (none, 0.1–4.9, and  $\geq 5.0$ ), passive smoking at work into 3 categories (never, former, and current), years of passive smoking at work into 3 categories (none, 1–5, and  $\geq 6$ ), age into 2 categories ( $<30$  and  $\geq 30$  years), gestation into 2 categories ( $<18$  and  $\geq 18$  weeks), parity into 2 categories (0 and  $\geq 1$ ), family income into 3 categories ( $<¥4,000,000$ ,  $¥4,000,000\text{--}5,999,999$ , and  $\geq ¥6,000,000$  per year), education into 3 categories ( $<13$ , 13–14, and  $\geq 15$  years), and dust mite antigen levels into 3 categories ( $-$ ,  $\pm$ , and  $+$  or  $++$ ). To examine whether the prevalence increased with smoking status, trend of association was evaluated using a logistic regression model assigning scores to the levels of the independent variable. Two-sided  $P < .05$  was considered statistically significant. All computations were performed using a software package (SAS version 8.2; SAS Institute Inc, Cary, NC).

#### RESULTS

The prevalences of asthma, atopic eczema, and allergic rhinitis (including cedar pollinosis) in the previous 12 months were 2.1%, 5.7%, and 14.1%, respectively, in 1,002 pregnant women. Regarding asthma, we were more interested in associations with asthma after the age of 18 years, which had a prevalence of 4.7%, than those with current asthma because the prevalence of current asthma was too low to have substantial statistical power. Of the 47 participants with asthma after the age of 18 years, 21 (44.7%) had received drug treatment for asthma between birth and the age of 12 years. Also, between birth and the age of 12 years, 52.6% of

participants currently with atopic eczema had received drug treatment for atopic eczema, and 10.6% of those with current allergic rhinitis had received drug treatment for rhinitis. Table 1 gives the distribution of selected factors in the 1,002 participants. The mean participant age was 29.8 years. Approximately 50% of the women were enrolled by the 17th week of gestation and 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. High mite antigen levels of  $10 \mu\text{g}/\text{m}^2$  or more were observed in 27% of participants.

Table 2 presents crude and adjusted ORs and 95% CIs in relation to active smoking status in 1,002 pregnant women. Compared with never smoking, current smoking was independently associated with a 2.7-fold increased prevalence of asthma after the age of 18 years, whereas former smoking was not measurably related to the prevalence of asthma after the age of 18 years after adjustment for age; gestation; parity; family history of asthma, atopic eczema, and allergic rhinitis; indoor domestic pets; family income; education; and the mite antigen level in house dust. A clear exposure-related relationship between cigarette smoking status and the prevalence of asthma after the age of 18 years was observed ( $P = .007$  for linear trend). A significant increased crude prevalence of asthma after the age of 18 years was found for smokers with 0.1 or more pack-years, showing a clear dose-response association with cumulative consumption of cigarettes. In the

Table 1. Distribution of Selected Factors in 1,002 Pregnant Women, Osaka Maternal and Child Health Study, Japan

Factor	Patients, No. (%)
Age, y	
<30	473 (47.2)
$\geq 30$	529 (52.8)
Gestation, wk	
<18	508 (50.7)
$\geq 18$	494 (49.3)
Parity of $\geq 1$	513 (51.2)
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, ¥/y*	
<4,000,000	301 (30.0)
4,000,000–5,999,999	403 (40.2)
$\geq 6,000,000$	298 (29.7)
Education, y	
<13	323 (32.2)
13–14	413 (41.2)
$\geq 15$	266 (26.6)
Mite antigen level in house dust†	
$-$	436 (43.5)
$\pm$	297 (29.6)
$+$ or $++$	269 (26.9)

\*US \$1 = ¥104.

†See the "Measurements" subsection for definitions of the antigen levels.

Table 2. Crude and Adjusted ORs and 95% CIs for Allergic Disorders in Relation to Smoking Status in 1,002 Pregnant Women, Osaka Maternal and Child Health Study, Japan

	Prevalence, No./total No. (%)	OR (95% CI)	
		Crude	Adjusted*
<b>Asthma after age 18 y</b>			
<b>Cigarette smoking</b>			
Never	23/697 (3.3)	1.00	1.00
Former	7/121 (5.8)	1.80 (0.70–4.09)	1.44 (0.54–3.44)
Current	17/184 (9.2)	2.98 (1.54–5.69)	2.66 (1.30–5.38)
<i>P</i> for linear trend	NA	.0009	.007
<b>Pack-years of smoking</b>			
None	23/697 (3.3)	1.00	1.00
0.1–4.9	11/143 (7.7)	2.44 (1.12–5.02)	2.16 (0.95–4.66)
≥5.0	13/162 (8.0)	2.56 (1.23–5.09)	2.10 (0.96–4.43)
<i>P</i> for linear trend	NA	.004	.03
<b>Current atopic eczema</b>			
<b>Cigarette smoking</b>			
Never	45/697 (6.5)	1.00	1.00
Former	7/121 (5.8)	0.89 (0.36–1.90)	1.02 (0.40–2.31)
Current	5/184 (2.7)	0.41 (0.14–0.94)	0.41 (0.14–1.03)
<i>P</i> for linear trend	NA	.06	.11
<b>Pack-years of smoking</b>			
None	45/697 (6.5)	1.00	1.00
0.1–4.9	5/143 (3.5)	0.53 (0.18–1.23)	0.52 (0.17–1.28)
≥5.0	7/162 (4.3)	0.65 (0.27–1.39)	0.78 (0.30–1.79)
<i>P</i> for linear trend	NA	.18	.36
<b>Current allergic rhinitis</b>			
<b>Cigarette smoking</b>			
Never	97/697 (13.9)	1.00	1.00
Former	21/121 (17.4)	1.30 (0.76–2.14)	1.24 (0.71–2.10)
Current	23/184 (12.5)	0.88 (0.53–1.42)	0.98 (0.57–1.62)
<i>P</i> for linear trend	NA	.83	.91
<b>Pack-years of smoking</b>			
None	97/697 (13.9)	1.00	1.00
0.1–4.9	22/143 (15.4)	1.13 (0.67–1.83)	1.18 (0.68–1.98)
≥5.0	22/162 (13.6)	0.97 (0.58–1.57)	1.01 (0.58–1.69)
<i>P</i> for linear trend	NA	.97	.85

Abbreviations: CI, confidence interval; NA, not applicable; OR, odds ratio.

\*Based on multiple logistic regression controlling for age (<30 and ≥30 years); gestation (<18 and ≥18 weeks); parity (0 and ≥1); family history of asthma, atopic eczema, and allergic rhinitis; indoor domestic pets; family income (<¥4,000,000, ¥4,000,000–5,999,999, and ≥¥6,000,000 per year); education (<13, 13–14, and ≥15 years); and mite antigen level in house dust (–, ±, and + or ++).

multivariate model, however, the positive association with 0.1 to 4.9 and 5.0 or more pack-years of smoking fell just short of the significance level, although the trend was statistically significant. Active smoking status and pack-years of smoking were not statistically significantly associated with the prevalence of current atopic eczema and allergic rhinitis.

Table 3 provides crude and adjusted ORs and 95% CIs for allergic disorders according to passive smoking exposure at home in the sample of 697 never-smoking pregnant women. After controlling for the potential confounding factors under study, there was no material association between passive smoking at home and the prevalence of asthma after the age of 18 years or current atopic eczema, although current passive smoking at home showed a tendency toward a positive relationship with current eczema ( $P = .07$  for linear trend).

Current passive smoking at home was independently associated with an increased prevalence of current allergic rhinitis; a positive linear trend was significant ( $P = .02$  for linear trend). Also, 0.1 to 4.9 pack-years of passive smoking at home were significantly related to a 1.9-fold increased prevalence of current allergic rhinitis, although the association with 5.0 or more pack-years of passive smoking at home was not statistically significant.

Results for passive smoking in the workplace are given in Table 4. Passive smoking at work was not statistically significantly associated with the prevalence of asthma after the age of 18 years and current atopic eczema. Current passive exposure to tobacco smoke in the workplace was independently associated with an increased prevalence of current allergic rhinitis, but a positive linear trend was not statisti-

Table 3. Crude and Adjusted ORs and 95% CIs for Allergic Disorders in Relation to Passive Smoking Status at Home in 697 Never-Smoking Pregnant Women, Osaka Maternal and Child Health Study, Japan

	Prevalence, No./total No. (%)	OR (95% CI)	
		Crude	Adjusted*
<b>Asthma after age 18 y</b>			
Passive smoking at home			
Never	5/249 (2.0)	1.00	1.00
Former	6/169 (3.6)	1.80 (0.53–6.33)	1.62 (0.46–5.88)
Current	12/279 (4.3)	2.19 (0.80–6.97)	1.90 (0.65–6.32)
P for linear trend	NA	.15	.26
Pack-years of passive smoking at home			
None	5/249 (2.0)	1.00	1.00
0.1–4.9	10/211 (4.7)	2.43 (0.85–7.90)	2.21 (0.74–7.43)
≥5.0	8/237 (3.4)	1.71 (0.56–5.71)	1.42 (0.44–4.95)
P for linear trend	NA	.39	.62
<b>Current atopic eczema</b>			
Passive smoking at home			
Never	13/249 (5.2)	1.00	1.00
Former	11/169 (6.5)	1.26 (0.54–2.90)	1.28 (0.53–3.05)
Current	21/279 (7.5)	1.48 (0.73–3.09)	2.02 (0.95–4.49)
P for linear trend	NA	.28	.07
Pack-years of passive smoking at home			
None	13/249 (5.2)	1.00	1.00
0.1–4.9	16/211 (7.6)	1.49 (0.70–3.23)	1.70 (0.76–3.84)
≥5.0	16/237 (6.8)	1.31 (0.62–2.84)	1.64 (0.74–3.72)
P for linear trend	NA	.49	.22
<b>Current allergic rhinitis</b>			
Passive smoking at home			
Never	25/249 (10.0)	1.00	1.00
Former	25/169 (14.8)	1.56 (0.86–2.82)	1.48 (0.80–2.73)
Current	47/279 (16.9)	1.82 (1.09–3.09)	1.89 (1.10–3.30)
P for linear trend	NA	.03	.02
Pack-years of passive smoking at home			
None	25/249 (10.0)	1.00	1.00
0.1–4.9	37/211 (17.5)	1.91 (1.11–3.32)	1.92 (1.10–3.40)
≥5.0	35/237 (14.8)	1.55 (0.90–2.71)	1.53 (0.87–2.73)
P for linear trend	NA	.13	.16

Abbreviations: CI, confidence interval; NA, not applicable; OR, odds ratio.

\*Based on multiple logistic regression controlling for age (<30 and ≥30 years); gestation (<18 and ≥18 weeks); parity (0 and ≥1); family history of asthma, atopic eczema, and allergic rhinitis; indoor domestic pets; family income (<¥4,000,000, ¥4,000,000–5,999,999, and ≥¥6,000,000 per year); education (<13, 13–14, and ≥15 years); and mite antigen level in house dust (–, ±, and + or ++).

cally significant. No significant dose-related association was found between years of passive smoking at work and the prevalence of current allergic rhinitis.

## DISCUSSION

In the analysis of baseline data from the prospective Osaka Maternal and Child Health Study among pregnant Japanese women, we found that current smoking, but not ETS exposure, was independently associated with an increased prevalence of asthma after the age of 18 years. However, a significant positive relationship between current passive smoking exposure at home and at work, but not active smoking, and the prevalence of current allergic rhinitis was observed. Neither active nor passive smoking was statistically significantly related to the prevalence of current atopic eczema.

The present findings are in agreement with previous observations<sup>1,7–12</sup> in adults showing a positive association between active smoking and asthma in both sexes or in women only but at variance with other studies showing an inverse<sup>3,5</sup> or no<sup>16</sup> association. The Obstructive Lung Disease in Northern Sweden Study<sup>1</sup> demonstrated that between 1986 and 1992, the period under study, 78 individuals who had been smokers in 1986 developed asthma. Of those 78 individuals, 21 stopped smoking in 1992. If the smoking habits in 1992 were used as independent variables, the effect of former smoking as a risk factor for asthma would increase and the effect of current smoking would decrease compared with smoking habits in 1986.<sup>1</sup> In the present study, the adjusted OR for comparison of active former smoking with never

Table 4. Crude and Adjusted ORs and 95% CIs for Allergic Disorders in Relation to Passive Smoking Status in the Workplace in 697 Never-Smoking Pregnant Women, Osaka Maternal and Child Health Study, Japan

	Prevalence, No./total No. (%)	OR (95% CI)	
		Crude	Adjusted*
<b>Asthma after age 18 y</b>			
Passive smoking at work			
Never	11/277 (4.0)	1.00	1.00
Former	9/344 (2.6)	0.65 (0.26–1.59)	0.62 (0.23–1.58)
Current	3/76 (4.0)	0.99 (0.22–3.28)	1.12 (0.24–3.98)
<i>P</i> for linear trend	NA	.66	.71
Years of passive smoking at work			
None	11/277 (4.0)	1.00	1.00
1–5	6/240 (2.5)	0.62 (0.21–1.66)	0.62 (0.20–1.73)
≥6	6/180 (3.3)	0.83 (0.28–2.23)	0.82 (0.26–2.34)
<i>P</i> for linear trend	NA	.63	.61
<b>Current atopic eczema</b>			
Passive smoking at work			
Never	21/277 (7.6)	1.00	1.00
Former	21/344 (6.1)	0.79 (0.42–1.49)	0.91 (0.46–1.78)
Current	3/76 (4.0)	0.50 (0.12–1.51)	0.33 (0.07–1.09)
<i>P</i> for linear trend	NA	.24	.15
Years of passive smoking at work			
None	21/277 (7.6)	1.00	1.00
1–5	18/240 (7.5)	0.99 (0.51–1.90)	0.98 (0.49–1.95)
≥6	6/180 (3.3)	0.42 (0.15–1.00)	0.43 (0.15–1.09)
<i>P</i> for linear trend	NA	.09	.13
<b>Current allergic rhinitis</b>			
Passive smoking at work			
Never	39/277 (14.1)	1.00	1.00
Former	38/344 (11.1)	0.76 (0.47–1.22)	0.71 (0.43–1.17)
Current	20/76 (26.3)	2.18 (1.17–3.99)	2.50 (1.29–4.76)
<i>P</i> for linear trend	NA	.13	.11
Years of passive smoking at work			
None	39/277 (14.1)	1.00	1.00
1–5	28/240 (11.7)	0.81 (0.48–1.35)	0.80 (0.47–1.37)
≥6	30/180 (16.7)	1.22 (0.72–2.04)	1.21 (0.69–2.11)
<i>P</i> for linear trend	NA	.54	.62

Abbreviations: CI, confidence interval; NA, not applicable; OR, odds ratio.

\*Based on multiple logistic regression controlling for age (<30 and ≥30 years); gestation (<18 and ≥18 weeks); parity (0 and ≥1); family history of asthma, atopic eczema, and allergic rhinitis; indoor domestic pets; family income (<¥4,000,000, ¥4,000,000–5,999,999, and ≥¥6,000,000 per year); education (<13, 13–14, and ≥15 years); and mite antigen level in house dust (–, ±, and + or ++).

having smoked was 1.44 (95% CI, 0.54–3.44), whereas the corresponding OR for current smoking was 2.66 (95% CI, 1.30–5.38), although there were only 24 women with asthma after the age of 18 years who had ever smoked. We could not evaluate the potential effects of such a self-selection bias in our results. Two cross-sectional studies<sup>8,9</sup> showed a higher prevalence of asthma among former smokers than among current smokers in males but not in females. Female patients with asthma may be less likely to quit smoking than their male counterparts. In our study, a significant positive dose-response relationship between pack-years of smoking and asthma after the age of 18 years, and a significant positive association with current smoking, may provide little support for the important effect of active smoking on asthma, although the adjusted ORs for 0.1 or more pack-years of smoking were not statistically significant.

Significant positive relationships between ever-smoking and the risk of noninfectious rhinitis and between former smoking and the prevalence of allergic rhinitis among men and women were observed in a prospective cohort study in Sweden<sup>4</sup> and in a cross-sectional study in Singapore,<sup>6</sup> respectively. Three previous cross-sectional studies in Sweden,<sup>5</sup> Norway,<sup>14</sup> and Switzerland<sup>15</sup> showed that the prevalence of lifetime or current allergic rhinitis was highest in nonsmokers, intermediate in former smokers, and lowest in current smokers. All of these results contradicted our results. To our knowledge, only 1 of the cross-sectional studies, the one in Norway,<sup>14</sup> investigated whether there was an association between active smoking and atopic eczema and found none. This is compatible with the present findings.

Two cross-sectional studies<sup>20,21</sup> in European countries demonstrated that ETS exposure at work or outside the home, but

not at home, was significantly associated with an increased prevalence of asthma in males and females. A cross-sectional study<sup>19</sup> in Sweden showed that workplace ETS exposure was significantly related to methacholine challenge-positive asthma that was reported to be symptomatic at work in men but not in women. A significantly increased OR for physician-diagnosed asthma in relation to domestic exposure to ETS was found only among males in a Swedish case-referent study.<sup>18</sup> These findings are partially consistent with the present results. Patients with asthma may have been likely to avoid ETS exposure. Also, family members in a household with patients with asthma and office coworkers of patients with asthma may have altered their smoking habits. This hypothesis would have led to an underestimation of values in our results. In addition, it may be difficult to detect a clear positive association between passive smoking exposure and asthma in a population with few patients with asthma.

The present findings are at variance with the few previous observations<sup>6,17,21</sup> showing no material relationship between ETS exposure and allergic rhinitis among adults of both sexes. The prevalence of allergic rhinitis is the highest of all allergic disorders in Japan.<sup>26-28</sup> Exposure to cedar pollen is likely to be ubiquitous in the entire country. In a cross-sectional study of Japanese adolescents in Osaka, there was a marginally significant positive relationship between residences facing major roads and the prevalence of allergic rhinoconjunctivitis, which suggested interactive effects between air pollutants and sensitization to cedar pollen.<sup>26</sup> Many chemical agents in ETS are known, including nicotine, carbon monoxide, benzene, formaldehyde, and acrolein.<sup>20</sup> The joint effect of cedar pollen and ETS exposure may be indicated in this study. To our knowledge, no study has evaluated the relationship between exposure to ETS and atopic eczema in adults. No statistically significant association between parental smoking and atopic eczema was observed in a cross-sectional study of Swedish children aged 3 to 15 years.<sup>5</sup>

The present investigation had methodological advantages in that study participants were homogeneous in terms of all being pregnant and in that we obtained detailed data on active and passive smoking, such as the duration of tobacco exposure, although objective measurements of ETS exposure, such as salivary, serum, and urine cotinine levels, were not available. A modest correlation between self-reported passive smoking and biomarkers of ETS exposure was found in previous studies, however.<sup>29,30</sup> Important weaknesses of this study should be taken into account when interpreting the results. Of a total of 3,639 eligible pregnant women in Neyagawa City, only 627 (17.2%) took part in this study. We were uncertain whether there was a difference between participants and nonparticipants in Neyagawa City because data on personal characteristics, such as age, socioeconomic status, and history of allergic disorders, among the nonparticipants were not available. Regarding the remaining 375 participants, we could not calculate the participation rate because the exact number of eligible women was not available. Also, we could not compare participants with nonparticipants in the 4 col-

laborating hospitals and 6 municipalities. Our participants were not representative of pregnant Japanese women in the general population, and the present findings may not be generalized. In fact, educational levels were higher in the present study population than in the general population. According to the 2000 population census of Japan,<sup>31</sup> the proportions of women aged 30 to 34 years in Osaka Prefecture with years of education of less than 13, 13 to 14, 15 or more, and unknown were 49.2%, 32.3%, 13.6%, and 4.9%, respectively. Active smoking status in our participants was likely to be the same as that in the general population, however. In a nationwide nutritional survey in 1998, percentages of never, former, and current smoking in women aged 20 to 29 years were 76.0%, 4.9%, and 19.1%, respectively.<sup>32</sup> It was not ascertained whether our study participants represented a different group in terms of passive smoking status and the confounders being studied. Because the definition of allergic disorders was based on drug treatment, there was probably a loss of milder cases of allergic disorders. In particular, females who want to become pregnant or who are pregnant might tend to avoid drugs. Patients with asthma might be aware of the possible ill effects of smoking exposure, owing to increased bronchial reactivity, whereas individuals with atopic eczema and allergic rhinitis might not be aware of such effects. The consequence would have given rise to an overestimation of our findings regarding asthma because of differential outcome misclassification and an underestimation of the results in relation to atopic eczema and allergic rhinitis due to nondifferential outcome misclassification. The nature of the present cross-sectional study prevents conclusions from being drawn about causality. In particular, we should be more cautious about our results related to asthma after the age of 18 years compared with those related to current eczema and rhinitis with respect to temporality. Approximately 90% of individuals with allergic rhinitis had not been treated with medications when they were 12 years or younger, whereas the onset of asthma occurred in childhood in approximately half of the patients with asthma. This fact may support a causal relationship between ETS exposure and allergic rhinitis.

This is the first epidemiologic study of the relationship between active and passive smoking exposure and allergic disorders in pregnant Japanese women. Further investigations with more precise exposure and outcome measurements are required to draw a conclusion regarding whether active smoking and ETS exposure increase the likelihood of asthma and allergic rhinitis, respectively, in adults.

#### ACKNOWLEDGMENTS

We thank the Neyagawa City government, Hirakata City government, Katano City government, Shijonawate City government, Kaizuka City government, Takaishi City government, Hannan City government, Neyagawa City Medical Association, Hirakata City Medical Association, and Kadoma City Medical Association for their valuable support; Kozo Uehara, PhD, Department of Research and Development, Shinto Fine Co Ltd, Osaka, Japan, for his helpful discussions;

and Tomoko Shibasaki, Nahoko Nishimura, and Naomi Takaoka for their assistance.

## REFERENCES

1. Rönmark E, Lundbäck B, Jönsson E, et al. Incidence of asthma in adults: report from the Obstructive Lung Disease in Northern Sweden Study. *Allergy*. 1997;52:1071-1078.
2. Chen Y, Dales R, Tang M, Krewski D. Sex-related interactive effect of smoking and household pets on asthma incidence. *Eur Respir J*. 2002;20:1162-1166.
3. Troisi RJ, Speizer FE, Rosner B, et al. Cigarette smoking and incidence of chronic bronchitis and asthma in women. *Chest*. 1995;108:1557-1561.
4. Hellgren J, Lillienberg L, Jarlstedt J, et al. Population-based study of non-infectious rhinitis in relation to occupational exposure, age, sex, and smoking. *Am J Ind Med*. 2002;42:23-28.
5. Hjerm A, Hedberg A, Haglund B, Rosén M. Does tobacco smoke prevent atopic disorders? a study of two generations of Swedish residents. *Clin Exp Allergy*. 2001;31:908-914.
6. Ng TP, Tan WC. Epidemiology of allergic rhinitis and its associated risk factors in Singapore. *Int J Epidemiol*. 1994;23:553-558.
7. Godtfredsen NS, Lange P, Prescott E, et al. Changes in smoking habits and risk of asthma: a longitudinal population based study. *Eur Respir J*. 2001;18:549-554.
8. Langhammer A, Johnsen R, Holmen J, et al. Cigarette smoking gives more respiratory symptoms among women than among men: the Nord-Trøndelag Health Study (HUNT). *J Epidemiol Community Health*. 2000;54:917-922.
9. Chen Y, Dales R, Krewski D, Breithaupt K. Increased effects of smoking and obesity on asthma among female Canadians: the National Population Health Survey, 1994-1995. *Am J Epidemiol*. 1999;150:255-262.
10. Torén K, Hermansson BA. Incidence rate of adult-onset asthma in relation to age, sex, atopy and smoking: a Swedish population-based study of 15813 adults. *Int J Tuberc Lung Dis*. 1999;3:192-197.
11. Larsson L. Incidence of asthma in Swedish teenagers: relation to sex and smoking habits. *Thorax*. 1995;50:260-264.
12. Krzyzanowski M, Lebowitz MD. Changes in chronic respiratory symptoms in two populations of adults studied longitudinally over 13 years. *Eur Respir J*. 1992;5:12-20.
13. Vesterinen E, Kaprio J, Koskenvuo M. Prospective study of asthma in relation to smoking habits among 14729 adults. *Thorax*. 1988;43:534-539.
14. Bakke P, Gulsvik A, Eide GE. Hay fever, eczema and urticaria in southwest Norway: lifetime prevalences and association with sex, age, smoking habits, occupational airborne exposures and respiratory symptoms. *Allergy*. 1990;45:515-522.
15. Wüthrich B, Schindler C, Medici TC, et al. IgE levels, atopy markers and hay fever in relation to age, sex and smoking status in a normal adult Swiss population. *Int Arch Allergy Immunol*. 1996;111:396-402.
16. McWhorter WP, Polis MA, Kaslow RA. Occurrence, predictors, and consequences of adult asthma in NHANESI and follow-up survey. *Am Rev Respir Dis*. 1989;139:721-724.
17. Leuenberger P, Schwartz J, Ackermann-Liebrich U, et al. Passive smoking exposure in adults and chronic respiratory symptoms (SAPALDIA Study). *Am J Respir Crit Care Med*. 1994;150:1222-1228.
18. Thorn J, Brisman J, Torén K. Adult-onset asthma is associated with self-reported mold or environmental tobacco smoke exposures in the home. *Allergy*. 2001;56:287-292.
19. Blanc PD, Ellbjär S, Janson C, et al. Asthma-related work disability in Sweden: the impact of workplace exposures. *Am J Respir Crit Care Med*. 1999;160:2028-2033.
20. Larsson ML, Loit HM, Meren M, et al. Passive smoking and respiratory symptoms in the FinEsS Study. *Eur Respir J*. 2003;21:672-676.
21. Janson C, Chinn S, Jarvis D, et al. Effect of passive smoking on respiratory symptoms, bronchial responsiveness, lung function, and total serum IgE in the European Community Respiratory Health Survey: a cross-sectional study. *Lancet*. 2001;358:2103-2109.
22. Miyake Y, Miyamoto S, Ohya Y, et al. Relationship between active and passive smoking and total serum IgE levels in Japanese women: baseline data from the Osaka Maternal and Child Health Study. *Int Arch Allergy Immunol*. 2004;135:221-228.
23. Oryszczyn MP, Annesi-Maesano I, Campagna D, et al. Head circumference at birth and maternal factors related to cord blood total IgE. *Clin Exp Allergy*. 1999;29:334-341.
24. Konishi E, Uehara K. Antigen levels of *Dermatophagoides* mites (Acari: Pyroglyphidae) in dust samples collected in homes of allergic patients. *J Med Entomol*. 1994;31:394-399.
25. Takai T, Yuuki T, Okumura Y, et al. 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;34:255-261.
26. Miyake Y, Yura A, Iki M. Relationship between distance from major roads and adolescent health in Japan. *J Epidemiol*. 2002;12:418-423.
27. Miyake Y, Yura A, Iki M. Breastfeeding and the prevalence of symptoms of allergic disorders in Japanese adolescents. *Clin Exp Allergy*. 2003;33:312-316.
28. Miyake Y, Yura A, Iki M. Cross-sectional study of allergic disorders in relation to familial factors in Japanese adolescents. *Acta Paediatr*. 2004;93:380-385.
29. Riboli E, Preston-Martin S, Saracci R, et al. Exposure of non-smoking women to environmental tobacco smoke: a 10-country collaborative study. *Cancer Causes Control*. 1990;1:243-252.
30. Delfino RJ, Ernst P, Jaakkola MS, et al. Questionnaire assessments of recent exposure to environmental tobacco smoke in relation to salivary cotinine. *Eur Respir J*. 1993;6:1104-1108.
31. Statistic Bureau, Ministry of Public Management, Home Affairs, Posts and Telecommunications. 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; 2002.
32. The Study Circle for Health and Nutrition Information. *The National Nutrition Survey in Japan*. Tokyo, Japan: Daiichi Shuppan; 2000.

Requests for reprints should be addressed to:  
Yoshihiro Miyake, MD, PhD  
Department of Public Health  
Fukuoka University School of Medicine  
Fukuoka 814-0180, Japan  
E-mail: miyake-y@cis.fukuoka-u.ac.jp



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

Yoshihiro Miyake, MD, PhD,<sup>a</sup> Satoshi Sasaki, MD, PhD,<sup>b</sup> Yukihiro Ohya, MD, PhD,<sup>c</sup> Shoichi Miyamoto, MBA,<sup>d</sup> Ichiro Matsunaga, ME,<sup>e</sup> Toshiaki Yoshida, PhD,<sup>e</sup> Yoshio Hirota, MD, PhD,<sup>d</sup> Hajime Oda, MD, PhD,<sup>e</sup> and the Osaka Maternal and Child Health Study Group\* *Fukuoka, Tokyo, and Osaka, Japan*

**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  $\alpha$  and  $\beta$ .<sup>1,2</sup> 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.<sup>3</sup> 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.<sup>1-5</sup> 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.<sup>6</sup> Another prospective study in Japan found a marginally significant inverse relationship between soy product intake and total mortality.<sup>7</sup>

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.<sup>8,9</sup> 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- $\alpha$ .<sup>10</sup> Philpott et al<sup>11</sup> 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

From <sup>a</sup>the Department of Public Health, Fukuoka University School of Medicine; <sup>b</sup>the Project of Scientific Evaluation of Dietary Reference Intakes, National Institute of Health and Nutrition, Tokyo; <sup>c</sup>the Division of Allergy, Department of Medical Specialties, National Center for Child Health and Development, Tokyo; <sup>d</sup>the Department of Public Health, Osaka City University School of Medicine; and <sup>e</sup>the Osaka Prefectural Institute of Public Health.

Supported by a Grant-in-Aid (13770206) for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology and Health and Labour Sciences Research Grants from the Ministry of Health, Labour, and Welfare, Japan.

\*Other members of the study group are listed in the Appendix.

Received for publication December 7, 2004; revised February 17, 2005; accepted for publication February 17, 2005.

Available online April 14, 2005.

Reprint requests: Yoshihiro Miyake, MD, PhD, Department of Public Health, Fukuoka University School of Medicine, Fukuoka 814-0180, Japan. E-mail: miyake-y@cis.fukuoka-u.ac.jp.

0091-6749/\$30.00

© 2005 American Academy of Allergy, Asthma and Immunology

doi:10.1016/j.jaci.2005.02.016

*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-m<sup>2</sup> 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.<sup>12,13</sup>

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.<sup>14</sup> Energy-adjusted intake by the residual method was used for the analyses.<sup>15</sup>

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).<sup>16,17</sup> Antigen levels were semiquantitatively classified with scores of  $- (<2 \mu\text{g}/\text{m}^2)$ ,  $\pm (5 \mu\text{g}/\text{m}^2)$ ,  $+$  ( $10\text{--}15 \mu\text{g}/\text{m}^2$ ), and  $++ (>35 \mu\text{g}/\text{m}^2)$ . 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 ( $<29$ ,  $29\text{--}31$ , and  $32+$  years), gestation into 3 ( $<15$ ,  $15\text{--}20$ , 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  $<4,000,000$ ,  $4,000,000\text{--}5,999,999$ , and  $6,000,000+$ /year), education into 3 ( $<13$ ,  $13\text{--}14$ , and  $15+$  years), dust mite allergen levels into 4 ( $-$ ,  $\pm$ ,  $+$ , 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 <sup>2</sup> )	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/m<sup>2</sup>), ± (5 µg/m<sup>2</sup>), + (10-15 µg/m<sup>2</sup>), and ++ (>35 µg/m<sup>2</sup>).

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)†
<b>Total soy product</b>			
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
<b>Tofu</b>			
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
<b>Tofu products</b>			
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
<b>Fermented soybeans</b>			
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
<b>Boiled soybeans</b>			
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
<b>Miso</b>			
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
<b>Miso soup</b>			
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)†
<b>Soy protein</b>			
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
<b>Daidzein</b>			
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
<b>Genistein</b>			
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 acids<sup>18-28</sup> and fruit and antioxidants<sup>27,28</sup> 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.<sup>29-31</sup> This figure is generally higher than in adolescents in Western countries.<sup>32</sup> 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  $\mu\text{g}/\text{d}$  and 3.9  $\mu\text{g}/\text{d}$ , 2.7  $\mu\text{g}/\text{d}$  and 1.7  $\mu\text{g}/\text{d}$ , and 4676  $\mu\text{g}/\text{d}$  and 7151  $\mu\text{g}/\text{d}$ , respectively.<sup>33</sup> The corresponding figures for the current study were 7264  $\mu\text{g}/\text{d}$  and 12,029  $\mu\text{g}/\text{d}$ , 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.<sup>29</sup>

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.<sup>34</sup> 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.<sup>35</sup> 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.<sup>36</sup> 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.<sup>19</sup> Japanese cedar pollinosis is a seasonal disorder with a high prevalence that is often undiagnosed.<sup>37</sup> 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<sub>H</sub>2 side of the immune response,<sup>38</sup> although Chaouat et al<sup>39</sup> 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<sub>H</sub>1/T<sub>H</sub>2 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.<sup>38</sup> 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.

We acknowledge the Neyagawa City Government, Hirakata City Government, Katano City Government, Shijonawate City Government, Kaizuka City Government, Takaishi City Government, Hannan City Government, Neyagawa City Medical Association, Hirakata City Medical Association, and Kadoma City Medical Association for their valuable support; Kozo Uehara, PhD, Department of Research and Development, Shinto Fine Co Ltd, Osaka, Japan, for helpful discussions; and Ms Tomoko Shibazaki, Nahoko Nishimura, and Naomi Takaoka for their assistance.

## 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.
- Kimira M, Arai Y, Shimoi K, Watanabe S. Japanese intake of flavonoids and isoflavonoids from foods. *J Epidemiol* 1998;8:168-75.
- Willitt 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, Gamer 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

Other members of the Osaka Maternal and Child Health Study Group are as follows:

Hideharu Kanzaki and Mitsuyoshi Kitada (Department of Obstetrics and Gynecology, Kansai Medical University); Yorihiro Horikoshi (Department of Obstetrics and Gynecology, Kansai Medical University Kori); Osamu Ishiko, Yuichiro Nakai, Junko Nishio, and Seiichi Yamamasu (Department of Obstetrics and Gynecology, Osaka City University Graduate School of Medicine); Jinsuke

Yasuda (Department of Obstetrics and Gynecology, Matsushita Memorial Hospital); Seigo Kawai (Department of Obstetrics and Gynecology, Hoshigaoka Koseinenkin Hospital); Kazumi Yanagihara (Yanagihara Clinic); Koji Wakuda (Department of Obstetrics and Gynecology, Fujimoto Hospital); Tokio Kawashima (Kyohritsu Women's Clinic); Katsuhiko Narimoto (Ishida Hospital Obstetrics, Gynecology); Yoshihiko Iwasa (Iwasa Women's Clinic); Katsuhiko Orino (Orino Lady's Clinic); Itsuo Tsunetoh (Tsunetoh Obstetrics and Gynecology); Junichi Yoshida (Yoshida Clinic); Junichi Ito (Ito Obstetrics and Gynecology Clinic); Takuzi Kaneko (Kaneko Sanfujinka); Takao Kamiya (Kamiya Ladies Clinic); Hiroyuki Kuribayashi (Kuribayashi Clinic); Takeshi Taniguchi (Taniguchi Hospital); Hideo Takemura (Kosaka Women's Hospital); and Yasuhiko Morimoto (Aizenbashi Hospital).





## Active and Passive Smoking and Tooth Loss in Japanese Women: Baseline Data from the Osaka Maternal and Child Health Study

KEIKO TANAKA, DDS, PhD, YOSHIHIRO MIYAKE, MD, PhD, SATOSHI SASAKI, MD, PhD, YUKIHIRO OHYA, MD, PhD, SHOICHI MIYAMOTO, MBA, ICHIRO MATSUNAGA, ME, TOSHIAKI YOSHIDA, PhD, YOSHIO HIROTA, MD, PhD, HAJIME ODA, MD, PhD, AND THE OSAKA MATERNAL AND CHILD HEALTH STUDY GROUP\*

**PURPOSE:** Many studies have shown a positive association between cigarette smoking and oral diseases. Few studies, however, have focused on the relationship between passive smoking exposure and oral health in adults. We investigated the association of active and passive smoking exposure with tooth loss in Japan.

**METHODS:** Study subjects were 1002 pregnant women. Tooth loss was defined as previous extraction of one or more teeth. Adjustment was made for age, gestation, parity, family income, education, and body mass index.

**RESULTS:** Of the 1002 subjects, 256 women had lost one or more teeth. Current light smoking was independently related to an increased prevalence of tooth loss, showing a significant exposure-related association with smoking status. A significant positive association of 8 or more pack-years of smoking with the prevalence of tooth loss was observed. Also, a significant positive relationship was found between current heavy passive smoking at home and tooth loss, but not with pack-years of passive smoking at home. No measurable association between passive smoking exposure at work and tooth loss was indicated.

**CONCLUSIONS:** The present findings suggest that passive as well as active smoking may be associated with an increased prevalence of tooth loss in Japanese young adult women.

*Ann Epidemiol* 2005;15:358–364. © 2005 Elsevier Inc. All rights reserved.

**KEY WORDS:** Cross-sectional Studies, Pregnant Women, Smoking, Tobacco Smoke Pollution, Tooth Loss.

### INTRODUCTION

A number of studies have shown a positive relationship between cigarette smoking and tooth loss (1–10), dental caries (6–8), and periodontal disease (6, 7, 9, 11, 12). Dental caries and periodontal disease, which is characterized by absorption of the alveolar bone and loss of soft tissue attachment to the tooth, are generally explained as the result of the action of microorganisms. Tooth loss mainly

results from severe dental caries or periodontal disease. It was reported in 1994 that in Japanese women caries was the most frequent reason for tooth extraction (60.7%), followed by periodontal disease (32.1%) (13). Tooth loss is considered to be the ultimate indicator of the status of dental disease.

In a longitudinal study among Swedish women aged 38 to 60 years, the mean number of teeth lost during the 12-year follow-up period was 3.5 and 2.1 among smokers and non-smokers, respectively (3). A cross-sectional study of Finnish subjects aged 31 years found a significant association between smoking and loss of six or more teeth (10). A cross-sectional study in Sweden showed a significantly larger number of decayed and filled tooth surfaces among smokers than non-smokers (7). A nationally representative cross-sectional survey of US civilians found that a history of smoking was significantly positively associated with periodontal loss of attachment (12). Saliva plays a critical role in the maintenance of oral health; it acts as a buffering agent when acids are produced, physically removes debris from tooth surfaces, and has immunological and bacteriostatic properties (14, 15). Heintze demonstrated that for cigarette smokers, the salivary buffer effect was significantly lower than for non-smokers, and that the numbers of lactobacilli and *Streptococcus mutans* were significantly higher in saliva of smokers than of non-smokers (16).

From the Department of Public Health, Fukuoka University School of Medicine, Fukuoka, Japan (K.T., Y.M.); Project of Scientific Evaluation of Dietary Reference Intakes, National Institute of Health and Nutrition, Tokyo, Japan (S.S.); Division of Allergy, Department of Medical Specialties, National Center for Child Health and Development, Tokyo, Japan (Y.O.); Department of Public Health, Osaka City University School of Medicine, Osaka, Japan (S.M., Y.H.); Osaka Prefectural Institute of Public Health, Osaka, Japan (I.M., T.Y., H.O.).

Address correspondence to: Keiko Tanaka, D.D.S., Ph.D., Department of Public Health, Fukuoka University School of Medicine, Fukuoka 814-0180, Japan. Tel.: +81-92-801-1011(Ext. 3315); Fax: +81-92-863-8892. E-mail: k-tanaka@fukuoka-u.ac.jp

\*Other members of the Osaka Maternal and Child Health Study Group are listed in the Appendix

This study was supported by a Grant-in-Aid (13770206) for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology and Health and Labour Sciences Research Grants from the Ministry of Health, Labour, and Welfare, Japan.

Received July 27, 2004; accepted December 21, 2004.

---

Selected Abbreviations and Acronyms

ETS = environmental tobacco smoke  
OMCHS = Osaka Maternal and Child Health Study  
BMI = body mass index  
OR = odds ratio  
CI = confidence interval

---

On the other hand, there is scarce epidemiological information regarding the relationship between exposure to environmental tobacco smoke (ETS) and oral health status (17-19). We know of only one epidemiologic study in adults of a relationship between exposure to ETS at home or at work and the prevalence of periodontal disease (17). In that study, a significant positive relationship between such exposure and periodontal disease among a US population that had never smoked was found (17). The aim of the present study is to examine the association of active and passive smoking with tooth loss among pregnant Japanese women using baseline data from the Osaka Maternal and Child Health Study (OMCHS).

---

## METHODS

### Study Population

The OMCHS is an ongoing prospective cohort study of risk factors for maternal and child health such as dental health, allergic disorders, and postpartum depression. The background and general procedure of the OMCHS have been described previously (20). In brief, the OMCHS requested that pregnant women complete a baseline survey, which was followed by several post-natal surveys. Eligible subjects were those women who became pregnant in Neyagawa City, which is one of 44 municipalities in Osaka Prefecture, a metropolis in Japan with a total population of approximately 8.8 million. Of 3639 eligible subjects, 627 pregnant women (17.2%) in Neyagawa City took part in this study between November 2001 and March 2003. Eight pregnant women who did not live in Neyagawa City but who had become aware of the present study at an obstetric clinic before August 2002 decided by themselves to participate. 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 three obstetric hospitals in three other municipalities; those 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.

### Questionnaire

In the baseline survey, the participants filled out a set of two self-administered questionnaires. The participants mailed the questionnaires to the data management center. Research technicians completed missing or illogical data by telephone interview.

One of the self-administered questionnaires elicited information on age, gestation, parity, family income, education, experience of extraction of permanent teeth excluding third molars, number of remaining teeth, smoking habits, and passive smoking exposure at home and at work. Tooth loss was defined as the extraction of one or more teeth. The other self-administered questionnaire was a validated self-administered diet history questionnaire that was used to assess dietary habits over a period of 1 month (21, 22), from which data on self-reported height and weight were obtained. Body mass index (BMI) was computed as body weight (kg) divided by the square of body height (m).

### Statistical Analysis

Age, gestation, parity, family income, education, and BMI were used as confounding variables. Both active and passive current smoking status were classified approximately at the median point. Cigarette smoking was classified into four categories (never, former, and current smoker consuming < 15 or 15+ cigarettes per day); pack-years of smoking into four (none, 0.1-2.9, 3.0-7.9, and 8.0+); passive smoking at home into four (never, former, and current passive smoker exposed to < 10 or 10+ cigarettes per day); pack-years of passive smoking at home into four (none, 0.1-2.9, 3.0-7.9, and 8.0+); passive smoking at work into four (never, former, and current passive smoker exposed intermittently or constantly); years of passive smoking at work into four (none, 1-3, 4-6, and 7+); age into three (< 29, 29-31, and 32+ years); gestation into three (< 15, 15-20, and 21+ weeks); parity into two (0 and 1+); family income into three (< 4,000,000; 4,000,000-5,999,999; and 6,000,000+ yen/year); and education into three (< 13, 13-14, and 15+ years). BMI was used as a continuous variable. Crude odds ratios (ORs) and their 95% confidence intervals (CIs) for associations between active or passive smoking exposure and the prevalence of tooth loss were estimated with logistic regression. Multiple logistic regression analysis was used to control for the potential confounding effects of the selected factors. Trends of association were assessed using logistic regression assigning scores to the levels of the independent variable. P values (two-sided) less than 0.05 were regarded as

statistically significant. The analyses regarding the effects of ETS exposure at home and at work on tooth loss were limited to the 679 persons who reported that they had never smoked. The SAS software package version 8.2 was used to conduct all the statistical analyses (SAS Institute, Inc., Cary, NC).

## RESULTS

Of the 1002 study subjects, 21.4% had lost one to four teeth and 4.2% had lost five or more teeth (Table 1). The distribution of selected confounders is shown in Table 2. The mean age of the subjects was 29.8 years, with approximately 30% being between 29 and 31 years. About 70% of the subjects participated in the study by the 20th week of gestation. Approximately 50% had a parity of one or more.

The prevalence values of tooth loss for never, former, and light (< 15 cigarettes per day) and heavy (15+ cigarettes per day) current smoking were 22.8%, 30.6%, 32.9%, and 32.4%, respectively (Table 3). The crude ORs for comparison of light and heavy current smoking with never smoking were 1.66 (95% CI, 1.00-2.70) and 1.62 (95% CI, 1.02-2.52), respectively, whereas there was no statistically significant association between former smoking and the prevalence of tooth loss. A significant positive exposure-related relationship between cigarette smoking status and tooth loss was observed (P for linear trend = 0.005). After adjusting for age, gestation, parity, family income, education, and BMI, the positive exposure-related relationship was slightly attenuated (P for linear trend = 0.01). Only current light smoking was independently associated with an increased prevalence of tooth loss (adjusted OR = 1.71; 95% CI, 1.02-2.83). Compared with never smoking, 8.0 or more pack-years of active smoking was significantly related to a 2.9-fold increased prevalence of tooth loss, showing a significant dose-response association with cumulative consumption of cigarettes (P for linear trend < 0.0001). Adjustment for confounding factors under study also slightly attenuated the positive association (adjusted OR = 2.35; 95% CI, 1.46-3.78; P for linear trend = 0.0009).

**TABLE 1.** Distribution of tooth loss in 1002 pregnant women, OMCHS, Japan

Number of teeth lost	Number of subjects (%)
0	746 (74.5)
1	85 (8.5)
2	57 (5.7)
3	29 (2.9)
4	43 (4.3)
5+	42 (4.2)

OMCHS = Osaka Maternal and Child Health Study.

**TABLE 2.** Distribution of selected factors in 1002 pregnant women, OMCHS, Japan

Factor	Number (%) or mean (SD)
Age (% years)	
<29	380 (37.9)
29-31	299 (29.8)
32+	323 (32.4)
Gestation (% weeks)	
<15	357 (35.6)
15-20	329 (32.8)
21+	316 (31.5)
Parity of one or more (%)	513 (51.2)
Family income (% yen/year)	
<4,000,000	301 (30.0)
4,000,000-5,999,999	403 (40.2)
6,000,000+	298 (29.7)
Education (% years)	
<13	323 (32.2)
13-14	413 (41.2)
15+	266 (26.6)
Body mass index (kg/m <sup>2</sup> )	21.4 (2.8)

OMCHS = Osaka Maternal and Child Health Study.  
SD = standard deviation.

Table 4 shows the association between passive smoking status and tooth loss among the 697 subjects who had never smoked. With respect to ETS exposure at home, 21.3% with never, 17.8% with former, 23.4% with current light (< 10 cigarettes per day), and 32.0% with current heavy (10+ cigarettes per day) passive smoking exposure have lost one or more teeth. Little difference was found between crude and adjusted ORs for each factor. Current heavy passive smoking at home was independently associated with an increased prevalence of tooth loss; a positive linear trend across the four categories of passive smoking at home was statistically significant (P for linear trend = 0.03). There was no measurable association of pack-years of passive smoking at home with the prevalence of tooth loss. The prevalence values of tooth loss for never, former, and current intermittent, and constant passive smoking exposure at work were 20.9%, 23.0%, 30.8%, and 25.0%, respectively. Current intermittent passive smoking at work was associated with a 1.9-fold increased prevalence of tooth loss, but without statistical significance. No material relationship was observed between years of passive smoking in the workplace and tooth loss.

## DISCUSSION

In the analysis of baseline data from the OMCHS among pregnant Japanese women, we found that current light cigarette smoking and 8 or more pack-years of smoking were independently associated with an increased prevalence of tooth loss. This finding showed a clear dose-response relationship with cumulative consumption of cigarettes. A

**TABLE 3.** Crude and adjusted odds ratios and 95% CIs for tooth loss in relation to active smoking status in 1002 pregnant women, OMCHS, Japan

Smoking status	Prevalence	Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI) <sup>a</sup>
<b>Active smoking</b>			
Never	159/697 (22.8%)	1.00	1.00
Former	37/121 (30.6%)	1.49 (0.97-2.27)	1.42 (0.91-2.20)
Current <15/day	27/82 (32.9%)	1.66 (1.00-2.70)	1.71 (1.02-2.83)
Current 15+/day	33/102 (32.4%)	1.62 (1.02-2.52)	1.62 (0.99-2.63)
P for linear trend		0.005	0.01
<b>Pack-years of smoking</b>			
None	159/697 (22.8%)	1.00	1.00
0.1-2.9	22/91 (24.2%)	1.08 (0.63-1.77)	1.22 (0.71-2.04)
3.0-7.9	32/120 (26.7%)	1.23 (0.78-1.90)	1.30 (0.81-2.04)
8.0+	43/94 (45.7%)	2.85 (1.83-4.44)	2.35 (1.46-3.78)
P for linear trend		<0.0001	0.0009

CI = confidence interval.

OMCHS = Osaka Maternal and Child Health Study.

<sup>a</sup>Adjusted for age (< 29, 29-31, and 32+ years), gestation (< 15, 15-20, and 21+ weeks), parity (0 and 1+), family income (< 4,000,000, 4,000,000-5,999,999, and 6,000,000+ yen/year), education (< 13, 13-14, and 15+ years), and a continuous variable for body mass index.

significant positive association was observed between current heavy passive smoking at home and tooth loss among those who had never smoked. However, exposure to ETS at work was not statistically significantly associated with tooth loss.

In Japan, the law that restricted smoking in public places was just enforced in 2004. At the point of data collection, it is likely that smokers in Japan could smoke relatively freely anywhere and that our study population would have many opportunities for exposure to tobacco smoke.

**TABLE 4.** Crude and adjusted odds ratios and 95% CIs for tooth loss in relation to passive smoking status at home and in the workplace in 697 never-smoking pregnant women, OMCHS, Japan

Passive smoking status	Prevalence	Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI) <sup>a</sup>
<b>Passive smoking at home</b>			
Never	53/249 (21.3%)	1.00	1.00
Former	30/169 (17.8%)	0.80 (0.48-1.31)	0.77 (0.46-1.27)
Current <10/day	36/154 (23.4%)	1.13 (0.69-1.82)	1.10 (0.67-1.82)
Current 10+/day	40/125 (32.0%)	1.74 (1.07-2.82)	1.79 (1.08-2.94)
P for linear trend		0.03	0.03
<b>Pack-years of passive smoking at home</b>			
None	53/249 (21.3%)	1.00	1.00
0.1-2.9	36/155 (23.2%)	1.12 (0.69-1.80)	1.11 (0.67-1.82)
3.0-7.9	28/123 (22.8%)	1.09 (0.64-1.82)	1.05 (0.61-1.77)
8.0+	42/170 (24.7%)	1.21 (0.76-1.92)	1.18 (0.73-1.89)
P for linear trend		0.44	0.55
<b>Passive smoking at work</b>			
Never	58/277 (20.9%)	1.00	1.00
Former	79/344 (23.0%)	1.13 (0.77-1.66)	1.05 (0.71-1.56)
Current, intermittently	16/52 (30.8%)	1.68 (0.85-3.19)	1.87 (0.92-3.66)
Current, constantly	6/24 (25.0%)	1.26 (0.44-3.16)	1.25 (0.43-3.19)
P for linear trend		0.21	0.22
<b>Years of passive smoking at work</b>			
None	58/277 (20.9%)	1.00	1.00
1-3	34/145 (23.5%)	1.16 (0.71-1.86)	1.21 (0.73-1.97)
4-6	29/128 (22.7%)	1.11 (0.66-1.82)	1.14 (0.67-1.91)
7+	38/147 (25.9%)	1.32 (0.82-2.10)	1.07 (0.64-1.76)
P for linear trend		0.29	0.74

CI = confidence interval.

OMCHS = Osaka Maternal and Child Health Study.

<sup>a</sup>Adjusted for age (< 29, 29-31, and 32+ years), gestation (< 15, 15-20, and 21+ weeks), parity (0 and 1+), family income (< 4,000,000, 4,000,000-5,999,999, and 6,000,000+ yen/year), education (< 13, 13-14, and 15+ years), and a continuous variable for body mass index.