

Association of Farming with the Development of Cedar Pollinosis in Japanese Adults

KOZUE NAKAMURA, PhD, CHISATO NAGATA, PhD, KEIKO WADA, PhD,
KAORI FUJII, BPHARM, TOSHIAKI KAWACHI, BHSc, NAOYOSHI TAKATSUKA, PhD, AND
HIROYUKI SHIMIZU, PhD

PURPOSE: Although cross-sectional studies have reported that the prevalence of allergy is reduced on a farm, few prospective studies were carried out on adults. We examined the association of experience of farming with occurrence of cedar pollinosis in a prospective cohort in Japan.

METHODS: A total of 5,698 men and 6,533 women, aged 35 to 69 at baseline in 1992, participated in the Takayama Study, a population-based prospective cohort study. Occupational history was assembled via a self-administered baseline questionnaire. To obtain information on cedar pollinosis, a follow-up questionnaire after 10 years from baseline was administered in 2002.

RESULTS: Compared with nonfarmers, farmers had a significantly reduced risk of cedar pollinosis after controlling for covariates (hazard ratio (HR): 0.61, 95% confidence interval (CI): 0.41, 0.90 in men; and HR: 0.31, 95% CI: 0.16, 0.60 in women). There was no significant association of cedar pollinosis with other occupations except for an increased risk of pollinosis among salesmen in multivariate analyses. We observed that other occupational exposures were not associated with the onset of cedar pollinosis after adjusting by covariates, except for a decreased risk of cedar pollinosis for woodworking in men.

CONCLUSIONS: These data suggest that exposures related to farming environment might be protective against cedar pollinosis.

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INTRODUCTION

In Japan, cedar pollinosis is a common allergy caused by the pollen of the cedar tree (*Cryptomeria japonica*) in spring. The symptoms include rhinitis and/or conjunctivitis, accompanied by pollen-specific immunoglobulin E (IgE) production. According to the most recent available data, the prevalence of cedar pollinosis in adults was 24.5% in the general population in urban areas and had increased 2.6-fold in the last couple of decades in Japan (1, 2).

Several cross-sectional studies have consistently indicated a lower prevalence of allergic diseases, such as asthma, allergic rhino-conjunctivitis, and atopic eczema, among people living in rural areas compared with those in urban areas worldwide (3–10). The different prevalence of allergic diseases according to locality (farm area or urban area) may be explained due to the exposure to microbes rich in farm. Recent findings have shown that pathogen-associated

molecular patterns (PAMPs) in bacteria may prevent allergies in early childhood and adulthood (11–13). A few prospective studies have been conducted to assess the association of rural or agricultural life with the occurrence of allergies in children. There were no prospective studies to assess the association between the farm environment and nasal allergies in adults. Cedar pollinosis, the most common nasal allergy in Japan, usually develops during adulthood. Therefore, it is worth investigating the association between farming and cedar pollinosis among adults in a longitudinal design. In the present study, we examined the association of farming with the occurrence of cedar pollinosis during a follow-up study in a cohort of Japanese individuals from the Takayama Study. We also examined the relation between other occupations and cedar pollinosis in Japanese men and women.

METHODS

Subjects for this study were cohort members from the Takayama study, a population-based cohort study conducted in Takayama, Gifu, Japan, in September 1992 as a baseline study. Takayama is a suburban city located approximately in the center of Japan and characterized by an inland climate. The main industries are agriculture (including dairy),

From the Department of Epidemiology and Preventive Medicine, Gifu University Graduate School of Medicine, Gifu, Japan.

Address correspondence to: Kozue Nakamura, PhD, Department of Epidemiology and Preventive Medicine, Gifu University Graduate School of Medicine; 1-1 Yanagido Gifu, Gifu 501-1194, Japan. Tel.: +81-58-230-6410; Fax: +81-58-230-6413. E-mail: kozuen@gifu-u.ac.jp.

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Selected Abbreviations and Acronyms

CI = confidence interval
HR = hazard ratio
PAMPs = pathogen-associated molecular patterns

woodworking, furniture making, forestry, and tourism. A total of 36,990 residents aged 35 years or older in Takayama were invited to the present study in 1992. A baseline questionnaire completed by the respondents in this cohort sought demographic information and details regarding occupation, smoking, diet, and medical and reproductive histories. Details of the methodology have been thoroughly described elsewhere (14). The final fixed baseline cohort consisted of 31,152 subjects: 14,427 men and 17,125 women. The final participation rate was 85.3%. Smokers were defined as those who had ever smoked over 20 packs of cigarettes in their life and classified into former and current smokers. Participants' height and weight at baseline were based on self-reports and used for the calculation of body mass index. The information on diet including alcohol consumption was derived from food frequency questionnaire that had been already validated. Physical activity was assessed by asking the average hours weekly participants had spent to carry out various kinds of activities during the last year in a validated questionnaire, and translated into a metabolic equivalent (MET) (15).

The study participants in the present study were restricted to those who were younger than 70 years old at the baseline ($n = 26,546$) and were tracked to a follow-up study in July 2002. Among them, 1,120 had died and 1,058 had moved away from Takayama between September 1992 and March 2000, as certified by the residential registry. Although we had lost access to residential registry data on deaths and moves for the remaining term of the follow-up through July 2002, we noted an additional 404 deaths from obituaries. In July 2002, after excluding the aforementioned participants who were deceased and had moved ($n = 2,582$), we mailed a follow-up questionnaire to 23,964 subjects to obtain information on their experience with cedar pollinosis. Among those to whom the follow-up questionnaire was mailed, 1,460 had moved, 18 had died (according to family members), and 51 were physically unable to answer. Of the remaining 22,435 persons, 14,975 (66.7%) responded to the follow-up questionnaire.

The information on individual work experience was obtained via the baseline questionnaire based on the following question: "Which type of job have you held the longest during your life?" According to replies to this question, we made seven job categories, household management, farming, manufacturing/crafting, desk work, sales/retail, business management, and professional.

Participants who might have been exposed to chemical agents, such as petroleum, pesticides, and organic solvents, which might have caused allergies were asked a further question: "Which types of job or workplace have you been in for over 10 years?" Participants were required to choose one job title, metals, mining, textiles, plastics, gasoline, chemicals, rubber, shipyard, farming, woodworking, automobile repair, pesticides, or paint manufacturing, if they had occupational exposure. To identify participants who had worked outside, one question in the follow-up questionnaire was provided: "Have you ever worked outside in the daytime?" If the reply was affirmative, the individual was defined as an outdoor worker. If negative, the individual was considered an indoor worker.

The questionnaire regarding cedar pollinosis was developed based on that reported by Endo et al. (16). Information was sought regarding four symptoms of cedar pollinosis: sneezing, nasal discharge, nasal obstruction, and eye irritation. A case of cedar pollinosis was defined as the existence of three of the four symptoms, with at least one symptom occurring in spring only. Before the follow-up study, this questionnaire had been validated through diagnosis by an otolaryngologist based on nasal discharge, nasal provocation test, intracutaneous test, and pollen-specific IgE positivity as the gold standard. The sensitivity and specificity were 0.80 and 0.65, respectively (17). The participants were required to report the age when each symptom had occurred for the first time. For individuals identified as having cedar pollinosis, the age at onset of the earliest symptom was defined as the age at onset of cedar pollinosis.

For the present analysis, participants who had experienced any type of cancer (62 men and 212 women) before the baseline were excluded. Furthermore, those known to have had pollinosis before the baseline according to the follow-up questionnaire (570 men and 1,001 women) and who did not respond completely to the questions regarding cedar pollinosis and occupation (344 men and 555 women) were also excluded. Hence, the population for the analysis consisted of 12,231 subjects (5,698 men and 6,533 women). To assess a risk of cedar pollinosis for the occupation except farming, subjects who had worked as farmers for the longest period in a lifetime were excluded because farmers indicated a reduced risk of cedar pollinosis. Informed consent was obtained from each participant. This study was approved by the local ethics board of the Gifu University Graduate School of Medicine.

Misclassification might have occurred because the age at onset of cedar pollinosis in follow-up questionnaire depended on the recall by participants. We also conducted analysis after excluding participants who reported the time of occurrence of cedar pollinosis within the first 3 years for the follow-up period and including those who reported the onset for 3 years before the baseline.

Statistical Analyses

The associations of cedar pollinosis with history of farming or other occupation at the baseline study were examined using a Cox proportional hazards model. Person-years of follow-up for each subject were calculated from the time of enrollment in the study (September 1992) to the date of onset of cedar pollinosis or the end of the study (July 2002), whichever came first. Analyses were carried out separately for men and women, because some job categories such as housewives were specific to women. Multivariate analysis was conducted using the covariates of age, smoking, and years of education as potential confounders of allergic rhinitis. All statistical analyses were carried out using SAS programs (SAS Institute, Cary, NC). Significance was defined as two-sided p less than 0.05.

RESULTS

Baseline demographics for both farmers and nonfarmers in our study are given in Table 1. The study population included 683 (12.0%) male and 425 (6.5%) female farmers. Both male and female farmers were more likely to be older, and participate in more physical activity than the other participants. In contrast, farmers were less likely to smoke and had less education. Marital status was not associated with farming in either sex.

During the 10-year follow-up period, a total of 1,001 participants (452 men and 549 women) were newly affected with cedar pollinosis. The association of farming with the risk of cedar pollinosis is given in Table 2. Among men and women, subjects who had the longest experience of farming in their life had a significantly decreased risk of onset of cedar pollinosis compared with nonfarmers after controlling for age (Hazard ratio [HR]: 0.59, 95% confidence interval [CI]: 0.41, 0.86 in men; HR: 0.33, 95% CI: 0.18, 0.62 in women). Additional adjustments for smoking and education did not alter the results substantially.

Employment in other jobs was not associated with the risk of cedar pollinosis in comparison with nonemployment in the corresponding work, except for sales in men, which in participants showed significantly increased risks of cedar pollinosis in both age-adjusted and multivariate models (Table 2). Thus participants who experienced sales were excluded when the analysis of the association of farming with cedar pollinosis was done. However, the reduced risk of cedar pollinosis for farming still remained.

Table 3 shows the risk of cedar pollinosis according to work in or out of doors. Men who worked outdoors and were not farmers had an increased risk of cedar pollinosis compared with indoor workers (HR: 1.30, 95% CI: 1.07–1.58). However, male farmers who worked outside were at a decreased risk of cedar pollinosis. Among the 683 men and 464 women in sales, 411 (60.2%) men and 91 (19.6%) women had worked outdoors. The risk of cedar pollinosis among salesmen was significantly increased regardless of indoor/outdoor status. HRs were 1.76 (95% CI: 1.20, 2.57) and 1.27 (95% CI: 1.03, 1.57) for salesmen working indoors and outdoors, respectively.

We also analyzed occupational exposure to substances that could cause allergies (Table 4). Some substances, such as rubber that contained fewer than five cases of pollinosis were omitted from the table. There was a significant and inverse association of greater than 10 years experience of farming with the occurrence of cedar pollinosis, after adjustments for age and other covariates, compared with no farming experience in both men and women. Men who were in furniture making and woodworking had a significantly reduced risk of cedar pollinosis after adjustment for covariates. Employment of women in the cotton or wool industry and furniture making or woodworking was not significantly associated with the onset of cedar pollinosis. Among men, there were increased but statistically insignificant associations of employment in automobile repair with the onset of cedar pollinosis.

TABLE 1. Baseline demographics of both farmers and nonfarmers

	Men			Women		
	Farmers	Nonfarmers	p Values*	Farmers	Nonfarmers	p Values*
Age (years)	55.1	52.1	<0.0001	55.8	52.0	<0.0001
BMI	22.7	22.6	0.88	22.4	22.1	0.07
Smoking (%)						
Never	22.2	16.6		96.2	85.5	
Former	28.6	28.7		0.8	3.5	
Current	49.3	54.7	<0.0001	3.0	11.0	<0.0001
Alcohol drinking (ml/day)	40.7	43.8	0.06	6.0	7.8	0.03
Physical activity (MET/week)	56.0	25.2	<0.0001	35.9	20.5	<0.0001
Education years over 15 years (%)	1.0	13.0	0.001	0.2	5.3	<0.0001

BMI = body mass index; MET = metabolic equivalents.

Values are crude means and percentages.

*Statistical significance level was considered to be $p < 0.05$.

TABLE 2. Risk of cedar pollinosis according to occupation

	Men				Women			
	Cases (n)	Person years	Age-adjusted HR (95% CI)	Multivariate HR (95% CI)*	Cases (n)	Person years	Age-adjusted HR (95% CI)	Multivariate HR (95% CI)*
Farming [†]								
No	422	46,945	1.00	1.00	539	57,106	1.00	1.00
Yes	30	6,227	0.59 (0.41–0.86)	0.59 (0.40–0.86)	10	4,124	0.33 (0.18–0.62)	0.32 (0.17–0.59)
Household management [†]								
No					316	32,379	1.00	1.00
Yes					223	24,727	1.00 (0.84–1.19)	0.98 (0.82–1.16)
Manufacturing [†]								
No	359	39,492	1.00	1.00	501	53,118	1.00	1.00
Yes	63	7,453	1.02 (0.78–1.33)	1.03 (0.78–1.36)	38	3,988	1.09 (0.78–1.52)	1.05 (0.75–1.46)
Deskwork [†]								
No	381	41,351	1.00	1.00	450	50,046	1.00	1.00
Yes	41	5,594	0.80 (0.58–1.10)	0.78 (0.56–1.08)	89	7,060	1.18 (0.94–1.49)	1.20 (0.95–1.52)
Sales [†]								
No	345	40,658	1.00	1.00	493	52,778	1.00	1.00
Yes	77	6,287	1.30 (1.01–1.66)	1.30 (1.01–1.66)	46	4,328	1.10 (0.81–1.49)	1.11 (0.82–1.50)
Business management [†]								
No	378	42,327	1.00	1.00	539			
Yes	44	4,618	1.24 (0.91–1.70)	1.28 (0.93–1.76)	0			
Professional [†]								
No	308	36,433	1.00	1.00	496	53,072	1.00	1.00
Yes	114	10,512	1.11 (0.89–1.38)	1.09 (0.88–1.36)	43	4,034	0.94 (0.69–1.29)	1.00 (0.72–1.37)

CI = confidence interval; HR = hazard ratio.

*Adjustment for age, smoking, and years of education.

[†]Worked the longest during participants' life; subjects who experienced farming were excluded.

Sensitivity analysis excluding subjects with the time of occurrence of this disease for the first 3 years from baseline, or including those who had developed 3 years before baseline revealed substantially unchanged results. For instance, HRs for male farmers were 0.66 (95% CI: 0.45, 0.96) in the former situation, and 0.65 (95% CI: 0.40, 1.04) in the latter, respectively.

DISCUSSION

The farm environment has been reported to reduce the risk of allergic diseases such as asthma, allergic rhinoconjunctivitis, and atopic eczema among both children and adults (3–10). In this prospective study, farming was

significantly and inversely associated with the occurrence of cedar pollinosis in both men and women compared with other job classifications or the occupations involving exposure to possible agents related to cedar pollinosis. As cedar pollinosis is directly induced by cedar pollen that exists outside, outdoor workers may suffer from cedar pollinosis more frequently than inside workers. Although farming is outdoor work, the risk reduction among farmers seems to be greater than possible increased risk due to exposure to cedar pollen outdoors. In fact, outdoor works other than farming were positively and significantly associated with risk of cedar pollinosis among men in our study.

Many previous cross-sectional studies have indicated that living on farm is associated with a reduced prevalence

TABLE 3. Risk of cedar pollinosis according to indoor or outdoor

	Men				Women			
	Cases (n)	Person years	Age-adjusted HR (95% CI)	Multivariate HR (95% CI)*	Cases (n)	Person years	Age-adjusted HR (95% CI)	Multivariate HR (95% CI)*
Indoor working	171	22,289	1.00	1.00	432	46,409	1.00	1.00
Outdoor working								
Farming	25	5,598	0.64 (0.43–0.99)	0.69 (0.45–1.06)	10	3,269	0.42 (0.22–0.78)	0.39 (0.21–0.74)
Other jobs	256	25,606	1.26 (1.04–1.53)	1.30 (1.07–1.58)	107	11,553	1.00 (0.81–1.23)	0.99 (0.80–1.23)

CI = confidence interval; HR = hazard ratio.

*Adjustment for age, smoking, and years of education.

TABLE 4. Risk of cedar pollinosis according to occupational exposure*

	Men				Women			
	Cases (n)	Person years	Age-adjusted HR (95% CI)	Multivariate HR (95% CI) [†]	Cases (n)	Person years	Age-adjusted HR (95% CI)	Multivariate HR (95% CI) [†]
Farming [‡]								
No	423	47,494	1.00	1.00	528	54,836	1.00	1.00
Yes	29	6,000	0.68 (0.47–0.99)	0.66 (0.45–0.96)	21	6,394	0.44 (0.29–0.69)	0.42 (0.27–0.65)
Metal processing [‡]								
No	432	51,770	1.00	1.00				
Yes	20	1,725	1.34 (0.86–2.10)	1.33 (0.85–2.08)				
Cotton or wool industry [‡]								
No	447	53,054	1.00	1.00	539	59,954	1.00	1.00
Yes	5	441	1.39 (0.57–3.34)	1.35 (0.56–3.25)	10	1,277	0.95 (0.51–1.78)	0.94 (0.50–1.77)
Plastics/petroleum /chemical/pesticides /paint industry [‡]								
No	440	51,461	1.00	1.00	544	60,603	1.00	1.00
Yes	12	2,033	0.63 (0.36–1.12)	0.63 (0.35–1.12)	5	628	0.86 (0.36–2.06)	0.83 (0.34–2.01)
Furniture making or woodworking [‡]								
No	417	46,728	1.00	1.00	525	57,777	1.00	1.00
Yes	35	6,768	0.69 (0.49–0.97)	0.69 (0.48–0.97)	24	3,453	1.09 (0.72–1.65)	1.07 (0.70–1.61)
Automobile repair [‡]								
No	429	51,684	1.00	1.00				
Yes	23	1,811	1.31 (0.86–1.99)	1.38 (0.90–2.10)				

CI = confidence interval; HR = hazard ratio.

*Occupational exposure was defined by job title that participants chose at baseline.

[†]Adjustment for age, smoking, and years of education.[‡]Worked for more than a decade.

of allergic diseases (5–10). To our knowledge, however, only two prospective studies have been conducted to examine the relationship of the farm environment with asthma in children (3, 4). The results of one study indicated that Canadian children living on a farm had a reduced risk of asthma compared with those in a rural nonfarming environment, with odds ratios of 0.22 and 0.39, respectively, for children with and without a family history of allergies (3). In the other study, parental farming was inversely and significantly related to allergic sensitization measured by a skin prick test in 1,150 elementary school children in Austria (4). So far, no prospective studies have been conducted on the relationship between the farm environment and allergic rhinitis in adults. The present prospective study is the first to assess the association between farming and the occurrence of cedar pollinosis in adults. Our result showing a significant inverse association between farming and cedar pollinosis does not contradict and in fact supports the findings of the previous studies. Some cross-sectional and prospective studies have suggested that dwelling on a farm and being exposed to a farm environment in early childhood are associated with a reduced risk of allergies later in life (3, 5, 6). However, one study in France reported that exposure to a farm environment during adulthood as well

as in early childhood was associated with a reduced risk of allergy (10).

Workers other than farmers, such as bakers, painters, chemical workers, and plastic product workers, are exposed to particulates that can induce an asthmatic reaction (18). In the present study, there were no associations between occupational exposures and cedar pollinosis except for farming and furniture making or woodworking in men. A decreased risk of cedar pollinosis was observed among farmers even though they are exposed to a variety of antigens, including organic dust, bacteria, pesticide, and chemical agents that can cause sensitization and allergic reactions. The decreased risk of cedar pollinosis among farmers could be explained by exposure to rich microbes on a farm. Microbes contain PAMPs, static structures in the cell wall, which may prevent allergies (11). Recent findings have shown that PAMPs, including lipopolysaccharides, may stimulate the signaling pathway through Toll-like receptors and induce higher innate immunological responses in the host (11–13). We observed that furniture making or woodworking in men had a significant decreased risk of cedar pollinosis. Fifty-six of 707 male woodworkers were also engaged in farming. It is also possible that exposure to microbes around timber may be associated with a decreased risk of cedar pollinosis in male woodworkers.

Salesmen were observed to have the increased risk of cedar pollinosis regardless of indoor/outdoor status in the present study. The products they sold or work environment might cause allergic rhinitis. Unfortunately, we could not obtain such detailed information. Studies assessing occupational information extensively are needed to elucidate the association of cedar pollinosis with sales.

There are several limitations of the present study. The limitations in the diagnosis of cedar pollinosis by self-reported symptoms should be considered. Cedar pollinosis is a prevalent seasonal allergy and is often undiagnosed in Japan. Therefore, we used a questionnaire that asked about symptoms related to this disease but not whether the subjects had been diagnosed by a physician. Although the specificity of the present questionnaire was not high in the validation study, no other validated questionnaire to identify cedar pollinosis has been published. Considering the relatively low specificity, some participants may be misclassified as “cases.” In addition, information on age at the onset was based on the long term recall. This might have caused misclassification, although the results were not altered by the inclusion or exclusion of cases who had the onset around the baseline. However, these misclassifications are likely to be independent of occupational status.

In the present study, we obtained information on neither childhood history of allergic diseases nor family history of allergies. The genetic selection bias should be considered if the prevalence of allergic tendency in farmers was originally lower than in nonfarmers because atopic parents or ancestors would have left their farms over generations. The observation that farmers had a significantly decreased risk of cedar pollinosis in the present analysis might be explained by this bias. However, we observed that farming was somewhat positively associated with a risk of asthma in men (HR: 1.36). It is unlikely that individuals who were insensitive to cedar pollinosis but not to asthma remained on farms. In addition, the observed increased risk of pollinosis among outdoor workers may suggest that a possible risk of cedar pollinosis would not greatly affect the selection of occupation. Nonetheless, we cannot deny the possibility of genetic selection bias. A prospective study including a younger generation is desirable for an allergic epidemiologic study.

Previous studies have suggested that residing on a farm and being exposed to a farm environment in early infancy are associated with a reduced risk of allergies later in life (3, 5, 6). The information on exposure to farming in childhood is necessary to demonstrate the protective effect of farming in adulthood. Unfortunately we did not have the information whether participants lived in a farm in childhood or not, especially that farming workers who did not stay in a farm during childhood but did during adulthood.

The low prevalence of allergic diseases has been reported to be consistently associated with farm livestock (12). According to governmental information, dairy farming is one of the main industries in Takayama. Many farmers in the present study were likely to be subject to a livestock environment (19).

The response rate was not high in the present study, and we did not obtain information on cedar pollinosis among subjects who had died or moved during the follow-up period. According to the present data, the percentage of male farmer respondents who responded to the follow-up questionnaire was similar to that of male nonfarmers, but female farmers were more likely to respond than other workers (data not shown). However, it is unlikely that female farmers who participated were less affected by cedar pollen than female nonfarmers who did not.

In summary, through a longitudinal study, we found a significant and inverse association between farming occupation and occurrence of cedar pollinosis in adults. To elucidate the association of farming with cedar pollinosis, further studies that seek individual detailed farming history information, such as type of agricultural work and exposure to organic dust, animal dander, plants, and insects containing microbe, are needed.

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REFERENCES

1. Okuda M. Epidemiology of Japanese cedar pollinosis throughout Japan. *Ann Allergy Asthma Immunol.* 2003;91:288–296.
2. Kaneko Y, Motohashi Y, Nakamura H, Endo T, Eboshida A. Increasing prevalence of Japanese cedar pollinosis: a meta-regression analysis. *Int Arch Allergy Immunol.* 2005;136:365–371.
3. Midodzi WK, Rowe BH, Majaesic CM, Senthilselvan A. Reduced risk of physician-diagnosed asthma among children dwelling in a farming environment. *Respirology.* 2007;12:692–699.
4. Horak F Jr, Studnicka M, Gartner C, Veiter A, Tauber E, Urbanek R, et al. Parental farming protects children against atopy: longitudinal evidence involving skin prick tests. *Clin Exp Allergy.* 2002;32:1155–1159.
5. Viinanen A, Munhbayarlah S, Zevgee T, Narantsetseg L, Naidansuren Ts, Koskenvuo M, et al. The protective effect of rural living against atopy in Mongolia. *Allergy.* 2007;62:272–280.
6. Adler A, Tager I, Quintero DR. Decreased prevalence of asthma among farm-reared children compared with those who are rural but not farm-reared. *J Allergy Clin Immunol.* 2005;115:67–73.
7. Riedler J, Eder W, Oberfeld G, Schreuer M. Austrian children living on a farm have less hay fever, asthma and allergic sensitization. *Clin Exp Allergy.* 2000;30:194–200.
8. Viinanen A, Munhbayarlah S, Zevgee T, Narantsetseg L, Naidansuren Ts, Koskenvuo M, et al. Prevalence of asthma, allergic rhinoconjunctivitis and allergic sensitization in Mongolia. *Allergy.* 2005;60:1357–1360.
9. Chen Y, Rennie D, Cormier Y, McDuffie H, Pahwa P, Dosman J. Reduced risk of atopic sensitization among farmers: the Humboldt study. *Int Arch Allergy Immunol.* 2007;144:338–342.

10. Kauffmann F, Oryszczyn MP, Maccario J. The protective role of country living on skin prick tests, immunoglobulin E and asthma in adults from the Epidemiological study on the Genetics and Environment of Asthma, bronchial hyper-responsiveness and atopy. *Clin Exp Allergy*. 2002;32:379–386.
11. Heederik D, Sigsgaard T. Respiratory allergy in agricultural workers: recent developments. *Curr Opin Allergy Clin Immunol*. 2005;5:129–134.
12. Braun-Fahrlander C. Environmental exposure to endotoxin and other microbial products and the decreased risk of childhood atopy: evaluating developments since April 2002. *Curr Opin Allergy Clin Immunol*. 2003;3:325–329.
13. Takeda K, Akira S. Toll receptors and pathogen resistance. *Cell Microbiol*. 2003;5:143–153.
14. Shimizu H. The Basic Report on Takayama Study. Gifu, Japan: Department of Public health, Gifu University School of Medicine; 1996.
15. Suzuki I, Kawakami N, Shimizu H. Reliability and validity of a questionnaire for assessment of energy expenditure and physical activity in epidemiological studies. *J Epidemiol*. 1998;8:152–159.
16. Endo T. Project report of the cedar pollinosis study for Science and Technology Agency. Tokyo, Japan: Research and Development Bureau of Science and Technology Agency; 2000. pp. 20–47.
17. Nagata C, Nakamura K, Fujii K, Kawachi T, Takatsuka N, Oba S, et al. Smoking and risk of cedar pollinosis in Japanese men and women. *Int Arch Allergy Immunol*. 2008;147:117–124.
18. Karjalainen A, Kurppa K, Virtanen S, Keskinen H, Nordman H. Incidence of occupational asthma by occupation and industry in Finland. *Am J Ind Med*. 2000;37:451–458.
19. Ministry of Agriculture, Forestry, and Fisheries. Preliminary Statistical Report on Agriculture, Forestry and Fisheries Production Output Value and Production Indices. Available at: <http://www.maff.go.jp/esokuhou/index.html>. Accessed: June 3, 2009.