Original Article

Analysis of Factors Associated with Cedar Pollen Sensitization and Development of Pollinosis in a Young Japanese Adult Population

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ABSTRACT

Background: Genetic and environmental factors are proposed to be involved in cedar pollen allergy sensitization and onset. The impact of these factors will provide key information for the prevention of cedar pollen sensitization and allergy onset, which we investigated in this cross-sectional study.

Methods: Subjects were 382 young adult volunteers who completed a self-administered questionnaire on self-reported subjective symptoms of pollinosis, physician-diagnosed pollinosis, and background factors. We also measured their serum IgE antibody titers specific for cedar, cypress, and mites. Factors associated with subjective symptoms, physician diagnosis, and the three specific antigens were determined using both univariate and multivariate analyses.

Results: Sensitization to cedar, cypress, and mites, defined as specific IgE levels of class 1 or above, was found in 78.8%, 64.4%, and 56.0% of subjects, respectively. The prevalence of cedar pollinosis was 41.2% based on subjective symptoms and 22.2% based on physician diagnosis. Factors associated with increased cedar pollen sensitization were mite sensitization, comorbid allergic rhinitis, and family history of cedar pollinosis. Risk-reducing factors for cedar pollen sensitization were keeping a cat, number of common colds, and hours of sleep. Risk-increasing factors for both subjective pollinosis symptoms and physician-diagnosed pollinosis were comorbid allergic rhinitis and family history of cedar pollinosis.

Conclusions: Sensitization to cedar pollen in this population was extremely high. Both common and distinct factors were associated with sensitization to pollen and with the development of pollinosis. The distinct factors were associated with sensitization to cedar and cypress antigens.

KEY WORDS:

association, factors, Japanese cedar pollinosis, sensitization, specific IgE antibody

Abbreviations:

FEIA, fluorescent enzyme immunoassay

CpG ODN, cytosine phosphate-guanosine oligodeoxynucleotides

INTRODUCTION

Seasonal allergic rhinitis caused by Japanese cedar pollen is the most common allergic disease in Japan and is considered a national affliction.[1] The prevalence of Japanese cedar pollinosis increased 2.6-fold between 1980 and 2000, and the prevalence differs considerably according to age[2] and degree of urbanization.[3] In a 2006-2007 survey of adults aged 20 to 49 years in Fukui Prefecture, the positive rate of serum Japanese cedar pollen specific IgE level above 0.7 (CAP RAST score of 2) was 55.5% and the prevalence of cedar pollinosis reported on a questionnaire was 36.7%.[4] Among adolescents, the prevalence of pollinosis, defined as the percentage of the population who were sensitized and had one or more seasonal rhinoconjunctival symptoms, was reported to be 28.7% in metropolitan areas in the year 2004.[3] In younger children, a 2003 epidemiological survey of allergic diseases among first-year junior high school students (age 11-12 years) in Wakayama Prefecture found that 48.6% of children had specific IgE antibodies against Japanese cedar pollen by MAST-26 (Hitachi Chemical, Tokyo, Japan)[5] and in 2015 sensitization to Japanese cedar pollen, defined as specific IgE class 1 or above by ImmunoCAP (Phadia, Uppsala, Sweden), was detected in 39% of lower--grade schoolchildren (aged 6-9 years).[6]

Japanese cedar pollinosis is a multifactorial disease, and genetic[7] and environmental factors[8-10] have been known to influence disease development. Familial clustering and intra-individual clustering suggest that overlapping genetic factors influence the development of allergic diseases. Many environmental factors have been investigated as influential factors for the development of allergic rhinitis. It has been reported that increased amounts of antigens,[8] living environment,[10] history of pet ownership, [11] smoking,[12-16] dietary habits,[17,18] and house dust mite sensitization[19] are associated with allergic rhinitis. Allergic rhinitis, and cedar pollen allergy in particular, imposes a high socioeconomic burden. Given the recent increases in cedar pollen allergy in Japan, effective preventive measures as well as effective treatments are important to determine. The elucidation of factors associated with the development of cedar pollen allergy will help effective strategies for prevention to be drawn up.

The development of allergic rhinitis occurs in two steps, sensitization to allergens and development of symptoms, and each step involves different mechanisms. Therefore, the influential factors for sensitization and symptomatic onset must be identified separately. This study sought to clarify the factors that influence the sensitization and symptomatic development of cedar pollinosis in a single population. Two parameters, self-reported subjective symptoms of cedar pollinosis and physician-diagnosed cedar pollinosis, were used to evaluate the development of

pollinosis. Moreover, sensitization to Japanese cypress and house dust mites was evaluated, and the factors associated with sensitization to each of the 3 allergens were determined.

METHODS

SUBJECTS AND ETHICAL CONSIDERATIONS

Initially, the subjects in this cross-sectional study were 590 volunteers (260 males and 330 females; age range 5-80 years) who were students, workers, or residents living in Mie Prefecture, Japan, regardless of whether they were symptomatic for cedar pollen allergy. We mounted posters to recruit volunteers. The study was conducted from August 2013 to March 2017 and adhered to the tenets of the Declaration of Helsinki. The study protocol was approved by Mie University Ethics Committee (No.2590), and written informed consent was obtained from all subjects or their legal guardians.

QUESTIONNAIRE

The questionnaire included questions to collect data in two broad categories: (1) general data on subject profiles and (2) data associated with allergies, and more specifically with cedar pollen allergies. The questionnaire (Supplementary Methods 1) included items on age, sex, occupation, and height and weight of the subject. The questions on allergies surveyed (1) self-reported subjective symptoms such as sneezing, nasal discharge and/or congestion, and itchy and/or teary eyes lasting for at least 2 weeks during the cedar pollen dispersal period (February-March) in the absence of a cold and (2) physician-diagnosed cedar pollen allergy. Data were collected on family history of cedar pollen allergy (among the subject's father, mother, siblings, grandfathers, grandmothers, and children) and on any concomitant and family history of allergic diseases (e.g., allergic rhinitis other than cedar pollen allergy, food allergies, hives, atopic dermatitis, oral allergy syndrome, and asthma). Also recorded was any past or concomitant history of sinusitis, angina, hyperlipidemia, diabetes, obstructive sleep apnea syndrome, cerebral infarction, or gastroesophageal reflux disease. Subjects also answered questions on the number of colds per year, history of smoking and passive smoking, number of cohabitants, current living environment, main site of daytime activity, frequency of playing outside during childhood, stress, regular exercise habits, and history of owning pets such as dogs and cats.

Questions about diet included the frequency of consumption of yogurt, meat, fish, fast food, beer, Japanese sake, wine, carbonated soft drinks, coffee, butter, eggs, fruit, margarine, milk, nuts, noodles and pasta, bread, rice, potatoes, vegetables, and soy

products. There were three possible answers for frequency of consumption: (1) very rarely, (2) 1-2 times per week, and (3) ≥ 3 times per week.

MEASUREMENT OF IgEs

Levels of specific IgE antibodies against cedar (*Cryptomeria japonica*), cypress (*Chamaecyparis obtusa*), and mites (*Dermatophagoides pteronyssinus*) and total IgE antibody levels were measured by CAP-FEIA (fluorescent enzyme immunoassay) (SRL, Tokyo, Japan). Sensitization to cedar pollen was defined as specific IgE levels of class 1 or above based on blood test results alone. Development of cedar pollen allergy was defined as (1) having pollinosis symptoms such as sneezing, nasal discharge and/or congestion, and itchy and/or teary eyes lasting for at least 2 weeks during the cedar pollen dispersal period every year (February-March) in the absence of a cold and (2) previous diagnosis of cedar pollen allergy by a physician.

STATISTICAL ANALYSIS

Univariate analysis with chi-square and Mann–Whitney *U* tests were used to determine sensitization to Japanese cedar pollen and development of pollinosis evaluated by subjective symptoms or physician diagnosis. Factors that exhibited strong correlations ($p < 0.2$) were further examined using multiple logistic regression analysis. Analyses were performed with SPSS statistical software version 21 (IBM, Chicago, IL). The same models were applied to identify factors associated with mites or cypress sensitization. A p value of less than 0.05 was considered statistically significant.

RESULTS

SUBJECTS

Questionnaires were received for a total of 590 subjects, and blood samples were taken from all subjects. Figure 1 shows the age distribution of the 590 subjects. Given the high number of subjects in their twenties, a subanalysis was performed among subjects in the age range 20–29 years (n = 382; 188 men, 194 women; mean age 23.6 years; age range 20-29 years). Mean height, body weight, and BMI of these 382 subjects were 166 cm, 59.4 kg, and 21.2, respectively. The findings reported below are confined to this young adult population only.

PREVALENCE

Among these 382 young adult subjects, 41.2% reported symptoms in the cedar pollen scattering period, and 22.2% had physician-diagnosed cedar pollinosis (Table 1). The

prevalence rates of comorbidities and family history of comorbidities such as allergic rhinitis other than cedar pollinosis, food allergy, urticarial rash, atopic dermatitis, oral allergy syndrome, and asthma are shown in Table 1. Of the 382 subjects, 9.9% reported they have the common cold ≥ 5 times per year. Smokers constituted 8.6%. Dogs and cats were kept as a pet by 37.2% and 13.9%, respectively. Sensitization to cedar, cypress, and mites, defined as specific IgE levels of class 1 or above, was present in 78.8%, 64.4%, and 56.0%, respectively (Table 1, Fig. 2).

FACTORS ASSOCIATED WITH CEDAR POLLINOSIS

The results of univariate analysis are shown in the Table 2, 3. Only those items that were statistically significant ($p < 0.05$) are shown.

The results of multiple logistic regression analysis are shown in Table 4, 5. As shown in Figure 3A, the factors associated with increased cedar pollen sensitization were mite sensitization, comorbid allergic rhinitis other than cedar pollinosis, and family history of cedar pollinosis (Fig. 3A). Three factors were associated with reduced risk of cedar pollen sensitization: keeping a pet cat, hours of sleep, and number of common colds per year. The factors associated with increased cypress pollen sensitization were serum total IgE level and family history of cedar pollinosis. Those associated with reduced risk of cypress pollen sensitization were number of common colds per year, BMI, stress, smoking, consumption of margarine, and consumption of fast foods (Fig. 3A).

The factors associated with increased house dust mite sensitization were serum total IgE level and comorbid asthma, while those associated with a reduced risk of mite sensitization were consumption of eggs and milk (Fig. 3A).

The factors associated with increased subjective symptoms of pollinosis were concomitant allergic rhinitis other than cedar pollen allergy and family history of cedar pollen allergy (Fig. 3B). Consumption of butter was a risk-reducing factor for subjective pollinosis symptoms (Fig. 3B).

The factors associated with physician diagnosis were concomitant allergic rhinitis other than cedar pollen allergy, family history of cedar pollinosis, and family history of conjunctivitis. History of consuming carbonated soft drinks was a risk-reducing factor for physician diagnosis (Fig. 3B).

DISCUSSION

The present study has been performed in Mie Prefecture. Geographically, Mie is situated close to the center of Japan, along the Pacific Ocean. The Prefecture has a

long, thin shape, being longer in the north-south direction than in the east-west direction. It takes approximately three hours to reach Tsu City (the capital of Mie) from Tokyo and 50 minutes from Nagoya. The annual average temperature for the Ise Plain is 15° C which is relatively warm for Japan. As a result, the annual cedar pollen count is larger than the average and the prevalence of cedar pollinosis is higher in Mie (33.3%) than the national average (26.5%).[20]

The rates of sensitization to cedar pollen and the prevalence of pollinosis differ considerably according to age, period, and degree of urbanization. In this study that focused on a young adult population in their twenties, the sensitization rate to Japanese cedar pollen was 78.8% and subjective symptoms were reported by 41.2% of subjects during the pollen season. The sensitization rate in the present study is higher than that in any other previous report.[3-6] The rate of sensitization and prevalence of cedar pollinosis depends on the age groups. This is partly because the cedar pollen count increased recently and sensitization started to occur in the younger ages than before.[20]

Sensitization to cedar pollen was defined as specific IgE levels of class 1 or above. Before we conducted statistics, we calculated percentage of subjects having pollinosis symptoms according to seven classes of cedar pollen specific IgE. As a result, subjects with class 1 had higher percentage of pollinosis than those with class 0. Thus we defined class 1 or more as sensitization.

The factors associated with increased cedar pollen sensitization were mite sensitization, comorbid allergic rhinitis other than cedar pollinosis, and family history of cedar pollinosis. According to a survey of first-grade schoolchildren conducted by Kanazawa et al,[21] children who were sensitized to mites but not to cedar had significantly elevated cedar pollen specific IgE levels compared with the group not sensitized to mites. This finding indicates that mite sensitization is very strongly associated with cedar pollen sensitization. Sensitization to house dust mites is the only factor associated with sensitization to cedar pollen in asymptomatic subjects.[19] Mite sensitization can potentially cause minimal persistent inflammation[22,23]; thus, repeated exposure to mite antigens at amounts that may not trigger allergies may still cause inflammation and a subsequent deficit in the defensive function of the nasal mucosa.

Two risk factors were common to both cedar pollen sensitization and the development of cedar pollinosis, regardless of the two different diagnostic criteria. The first risk factor was concomitant allergic rhinitis other than cedar pollen allergy. Inflammation of the nasal mucosa lowers the defensive function of the nasal epithelium and facilitates the entry of cedar pollen allergens into the body; increased allergen levels within the body are hypothesized to increase the likelihood of sensitization. In addition,

cells such as eosinophils and neutrophils infiltrate the nasal mucosa, thereby increasing sensitivity in patients with allergic rhinitis. This is suggested to increase the likelihood of a cedar pollen allergy developing because the amount of cedar pollen allergens would be smaller in the allergic mucosa than that required to trigger allergy in normal mucosa.[22] The second risk factor common to sensitization and development was family history of cedar pollinosis, which has previously been reported to be an important risk factor for both.[24,25] One reason may be the greater likelihood of genetic polymorphisms shared by blood relatives. Various genetic polymorphisms are associated with allergic rhinitis. These specifically include interleukin-33[7], which causes allergic inflammation by inducing eosinophil chemotaxis and cytokine production, and the expression of filaggrin,[26] which is important for skin barrier function.

The present study revealed some protective factors against sensitization to cedar and cypress. These included the number of common colds, hours of sleep, keeping a cat, and smoking. One of the most striking findings in this study was that the number of colds inversely correlated with sensitization to cedar (OR: 0.186, 95%CI: 0.078-0.448) and cypress (OR: 0.324, 95% CI: 0.141-0.743). The sensitization rate of those who have the common cold ≥ 5 times per year was 60.5%, while it was 80.8% in those who have colds < 5 times. We defined susceptibility to cold as having cold five times or more per year, because it is reported that the common cold is estimated to occur an average of 2–5 times for adults in the general healthy population.[27] To our knowledge, the inverse correlation between the sensitization to pollen antigens and the number colds has not been reported before in the literature. It is believed that wheezing associated with viral infections is a pivotal risk factor for the development of asthma.[28] However, some viral infections are reported to protect against persistent IgE sensitization,[29] and certain viral infections caught during the sensitization and challenge phases reduce the development of delayed eosinophilic allergic rhinitis in BALB/c mice.[30] Allergic rhinitis was reportedly associated with decreased expression of TLR9 in sinonasal epithelial cells.[31]

The above results have implications for the treatment of cedar pollinosis. Microbial factors likely modulate nasal innate immunity to maintain homeostasis. An approach targeting TLR9 by synthetic cytosine phosphate-guanosine oligodeoxynucleotides (CpG ODN) is a promising new treatment paradigm for modulating the immune response.[32] A clinical trial of immunotherapy with a ragweed-TLR9 agonist vaccine in adults allergic to ragweed has been proven successful.[33] Animal models have elucidated the mechanism of action of this therapy. CpG ODN is likely recognized by TLR9 on conventional dendritic cells and alveolar

278 macrophages, which produce mRNA encoding IL-12. IL-12 is necessary for the
279 subsequent production of innate and adaptive interferon-γ.[34] Mice that received CpG
280 showed reduced IgE antibody production at both neonatal and adult stages.[35]
281 In this study, keeping a cat was found to have a protective effect against
282 sensitization to cedar pollen (OR: 0.418, 95% CI 0.196–0.892). Current cat ownership
283 was related to significantly lower rates of allergic rhinitis (adjusted OR [aOR]: 0.71,
284 95% CI 0.57-0.89) and Japanese cedar pollinosis (aOR: 0.57, 95% CI 0.44-0.75).
285 However, there was no association between the prevalence of allergies and dog
286 ownership.[11] It remains unclear why the association observed with cats did not extend to
287 dogs. However, owning a cat has been shown to result in the accumulation of large
288 amounts of endotoxins in the living environment (OR: 1.91; 95% CI: 1.43-2.55),[10] and
289 there is a potentially larger bacterial load, including that of colon bacilli, indoors. The
290 reason why keeping a cat has a protective effect only to cedar pollen but not mite is
291 currently unknown and should be investigated in the future study.
292 In this study, smoking was a protective factor for sensitization to cypress
293 (OR:0.338, 95% CI: 0.139-0.821). Current smokers were at a significantly lower risk
294 of cedar pollinosis among men (hazard ratio [HR]: 0.64, 95% CI: 0.50-0.83) and women
295 (HR: 0.64, 95% CI: 0.47-0.88).[15] Strikingly, it has been reported that passive smoking
296 was also related to a significantly lower rate of allergic rhinitis (aOR: 0.83, 95% CI:
297 0.77-0.89) and Japanese cedar pollinosis (aOR: 0.81, 95% CI: 0.74-0.88).[11] The
298 underlying mechanism is likely to be cigarette smoke-mediated inhibition of
299 inflammatory cytokine production and T cell suppression, which would also trigger
300 sensitization.[12,13] In the present study, we were unable to detect an association between
301 allergy onset and history of smoking; however, Eriksson *et al.* previously reported that
302 the prevalence of allergic rhinitis was significantly lower in males with a history of
303 smoking.[14] Although smoking has a protective effect against allergic rhinitis, active,
304 passive, and electronic cigarette smoking is associated with asthma in adolescents.[16]
305 Duration of sleeping hours was also a protective factor. The present result
306 means the negative correlation between the duration of sleeping hours and the
307 sensitization rate, which indicates that short sleeping hours may increase risk of cedar
308 pollen sensitization. Although the precise mechanism is unclear, it is known that sleep
309 deprivation has detrimental effects on metabolic and immune regulation.[36] Zhang et al.
310 reported that short sleep duration is associated with the risk of sensitization to food and
311 aero allergens in rural Chinese adolescents.[37] Thus, it is probable that risk of allergic
312 sensitization can be reduced by appropriate guidance on sleep duration.
313 This study showed an association between consuming several foods and

decreased sensitization and development of pollinosis. Eggs and milk were inversely associated with sensitization to mites, and fast foods and margarine were inversely associated with sensitization to cypress. Butter and carbonated drinks were inversely associated with subjective symptoms and physician-diagnosed pollinosis, respectively. Reportedly, an increased risk of rhinoconjunctivitis was associated with the consumption of fast foods, margarine, and butter and a decreased risk with eggs and milk.[17] The reason why fast foods, margarine, and butter were associated with reduced rates of sensitization and pollinosis is unclear. It is possible that individuals sensitized to pollen and those with pollinosis avoided consuming these foods.

Although our results showed that the consumption of carbonated soft drinks was a protective factor against pollinosis based on physician diagnosis, no previous reports support this finding. Carbonated water may promote sympathetic nerve activity and ease the symptoms of allergic rhinitis such as nasal discharge and/or congestion, which are associated with parasympathetic nerve activation, thus delaying the onset of pollinosis. However, it will be a challenge to determine the mechanism underlying the apparent protective factor of consuming soft drinks 1-2 times per week.

Total IgE level, which was not identified as a risk factor for cedar pollen sensitization, was found to be associated with mite sensitization. Total IgE level can be used to estimate the contribution of an individual's characteristics to IgE antibody production and the strength of that individual's predisposition to atopy. Thus, our results demonstrate that although predisposition to atopy was not associated with the development of cedar pollen sensitization, mite sensitization was more likely to occur in people who exhibited a stronger predisposition to atopy. Our results showed that there is a causal relationship between mite IgE and cedar pollen sensitization. This was previously confirmed by studies showing that mite sensitization, which appears to be associated with a predisposition to atopy, occurs at a younger age than cedar pollen sensitization.[38,39]

One of the limitations of this study is that we did not consider the specialities of physicians who made diagnosis of pollinosis. Diagnosis of cedar pollinosis may be different between specialized ENT physicians and general family physicians.

Skin prick test is commonly used for the detection of causative allergen because of the high sensitivity, rapidity and inexpensiveness. However, allergen-specific IgE blood assay is widely used for clinics in our country and we also used serum IgE in this study. The major reason for this is no risk of severe allergic reaction in serum IgE measurement. However, serum IgE measurement may result in underestimation of sensitization status to allergens.

The sensitization rate to cedar pollen in a young Japanese adult population was extremely high. Both common and distinct factors were associated with sensitization to pollen and the development of pollinosis. Distinct factors were associated with sensitization to cedar and cypress antigens.

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Figure legends

Fig. 1. Age distribution of the 590 subjects in this study. Given the large number of subjects in their twenties, a subanalysis was performed among subjects in the age range 20–29 years.

Fig. 2. Distribution of specific IgE classes of the three antigens cedar, cypress, and mite among 382 subjects. Sensitization to cedar (*Cryptomeria japonica*), cypress (*Chamaecyparis obtusa*), and mites (*Dermatophagoides pteronyssinus*) was found in 78.8%, 64.4%, and 56.0% of subjects, respectively.

Fig. 3. Factors linked to sensitization to house dust mites, cedar pollen, and cypress **(A)**. Factors linked to self-reported subjective symptoms and physician diagnosis of Japanese cedar pollinosis **(B)**. Upward arrows indicate positively correlated factors and downward arrows indicate negatively correlated factors.

Table 1. Prevalence of antigen sensitization, cedar pollinosis, comorbidities, family history, and lifestyle among young Japanese adults aged 20-29 years (n = 382)

		%	Present	Absent
Sensitization	*Dermatophagoides pteronyssinus*	56.0	214	168
	Cryptomeria japonica	78.8	301	81
	Chamaecyparis obtusa	64.4	246	136
Self-reported symptoms of cedar pollinosis		41.2	160	222
Physician-diagnosed cedar pollinosis		22.2	85	297
Comorbidity	Allergic rhinitis	26.2	100	282
	Food allergy	7.9	30	352
	Urticaria	17.0	65	317
	Atopic dermatitis	21.2	81	301
	Oral allergy syndrome	4.5	21	361
	Asthma	12.8	49	333
Family history	Cedar pollinosis	68.8	263	119
	Allergic rhinitis	32.3	125	257
	Asthma	15.2	58	324
	Atopic dermatitis	18.6	71	311
	Conjunctivitis	4.7	18	364
	Food allergy	16.2	62	320
	Oral allergy syndrome	2.9	11	371
Catching the common cold ≥ 5 times per year		9.9	38	344
Smoking		8.6	33	349
Keeping a pet dog		37.2	142	240
Keeping a pet cat		13.9	53	329

Table 2. Result of univariate analysis on sensitization to three antigens

		Mites (P value)	Cedar (P value)	Cypress (P value)
Total IgE		0.000	0.000	0.000
Mite IgE class		NS	0.000	0.004
Cedar IgE class		0.000	NS	NS
Age		NS	NS	0.020
Body weight		NS	NS	0.045
BMI		NS	NS	0.014
Asthma		0.000	0.006	NS
Food allergy		0.006	0.013	0.024
Atopic dermatitis		0.000	0.005	0.001
Allergic rhinitis other than cedar pollinosis		0.000	0.001	NS
GERD		0.023	NS	NS
Otitis media with effusion		NS	0.006	NS
Family history	Cedar pollinosis	NS	0.004	0.000
	Asthma	0.015	NS	NS
	Atopic dermatitis	0.029	NS	NS
Smoking		0.043	NS	0.017
Keeping a pet cat		NS	0.037	NS
Number of colds		NS	0.004	0.002
Fast food		NS	NS	0.042
Margarine		NS	NS	0.025
Carbonated drinks		NS	NS	0.006
Vegetables		NS	0.013	NS
Eggs		0.047	NS	NS
Milk		0.006	NS	NS

BMI, body mass index; GERD, gastroesophageal reflux disease;NS, not significant

Table 3. Result of univariate analysis on pollinosis symptoms and diagnosis

		Subjective symptoms (P value)	Physician diagnosis (P value)
Food allergy		0.036	NS
Allergic rhinitis other than cedar pollinosis		0.000	0.000
OAS		NS	0.004
Family history	Cedar pollinosis	0.000	0.001
	Atopic dermatitis	NS	0.023
	Conjunctivitis	0.008	0.000
	OAS	0. 035	0.009
Keeping dogs as pets		0.024	NS
Meat		0.043	NS
Butter		0.014	NS
Carbonated drinks		NS	0.003

OAS, oral allergy syndrome; NS, not significant

Table 4. Result of multiple regression analysis on sensitization to three antigens

		House dust mites		Japanese cedar		Japanese cypress	
		Odd ratio (95%CI)	P value	Odd ratio (95%CI)	P value	Odd ratio (95%CI)	P value
Total IgE		1.005 (1.003-1.007)	0.000		NS	1.005 (1.003-1.007)	0.000
Mite IgE class			NA	1.571 (1.311-1.882)	0.000		NS
BMI			NS		NS	0.900 (0.821-0.987)	0.025
Asthma		8.067 (2.504-25.988)	0.000		NS		NS
Allergic rhinitis other than cedar pollinosis			NS	3.182 (1.351-7.494)	0.008		NS
Family history of cedar pollinosis			NS	2.8769 (1.608-5.142)	0.000	2.474 (1.456-4.203)	0.001
Keeping cats as pets			NS	0.418 (0.196-0.892)	0.024		NS
Hours of sleep			NS	0.666 (0.480-0.925)	0.015		NS
Number of colds			NS	0.186 (0.078-0.448)	0.000	0.324 (0.141-0.743)	0.008
Smoking			NS		NS	0.338 (0.139-0.821)	0.017
Stress			NS		NS	0.514 (0.309-0.854)	0.010
Fast food	≥3 per week		NS		NS	0.025 (0.001-0.683)	0.029
Margarine	1-2 per week		NS		NS	0. 321 (0.107-0.961)	0.042
Eggs	1-2 per week	0.286 (0.094-0.871)	0.028		NS		NS
Milk	≥ 3 per week	0.446 (0.236-0.843)	0.013		NS		NS

BMI, body mass index; CI, confidence interval; NS,not significant; NA, not applicable

Table 5. Result of multiple regression analysis on pollinosis symptoms and diagnosis

		Subjective symptoms		Physician diagnosis	
		Odds ratio (95%CI)	P value	Odds ratio (95%CI)	P value
Allergic rhinitis other than cedar pollinosis		2.799 (1.696-4.619)	0.000	4.204 (2.536-7.256)	0.000
Family history	Cedar pollinosis	3.539 (2.132-5.876)	0.000	2.482 (1.282-4.802)	0.007
	Allergic conjunctivitis		NS	4.289 (1.481-12.416)	0.007
Butter	≥ 3 per week	0.294 (0.126-0.685)	0.005		NS
Carbonated drinks	1-2 per week		NS	0.483 (0.261-0.896)	0.021

CI, confidence interval; NS, not significant

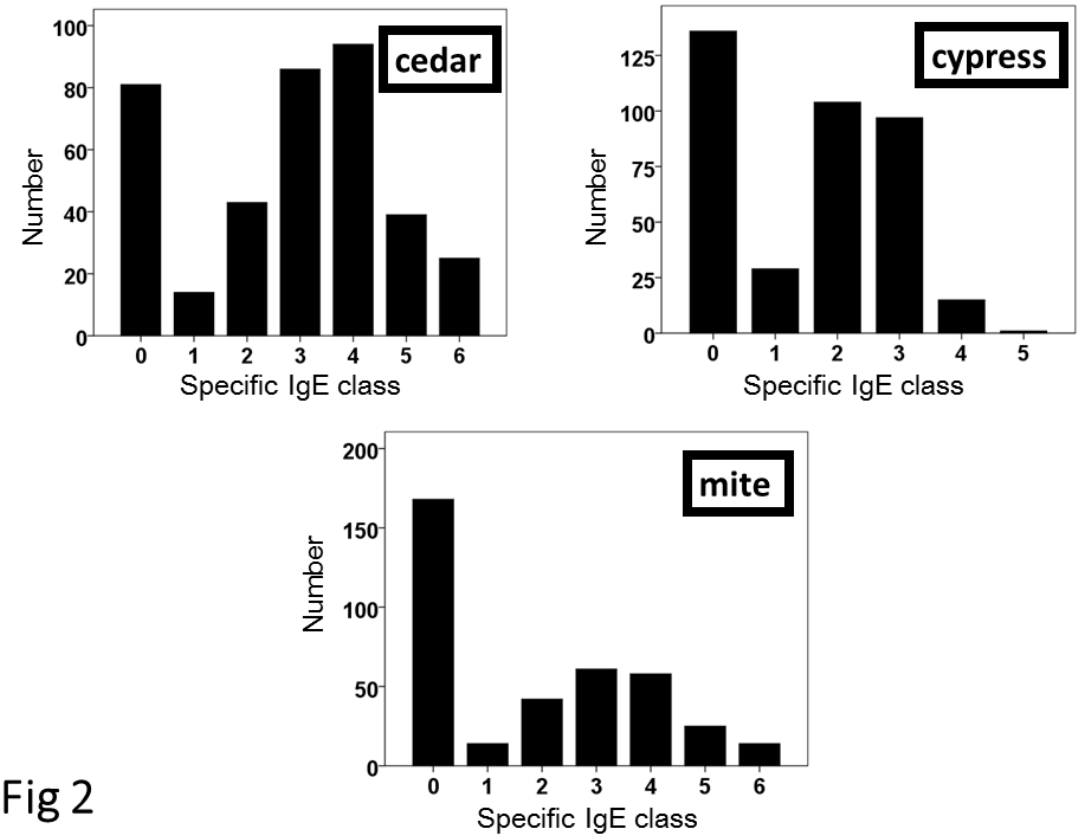
cedar
Number
Specific IgE class
cypress
Number
Specific IgE class
mite
Number
Specific IgE class

Fig 2

Medical interview sheet

This medical interview sheet is for the clinical examination: "Research on Sensitization and development of cedar pollinosis"
Please fill out the form with☑ and also write something if necessary
Personal information will be protected..

Date		year		month		Day	
age		Age	work		Have work		
gender		Male			No work (housework etc)		
		Female			student		
height		cm	weight		kg	Residing city	

I. Asking about your heath condition including allergy

1. Have you ever had symptoms of sneezing, watery rhinorrhea, nose blocking, itchy eyes, tearing for more than two weeks continuously in February to March (time of cedar pollen scattering) without having cold?

	No
	Every year
	sometimes
	This year for the first time

2. Have you ever been told that you have cedar allergy by a medical doctor?

	No
	I didn't see a doctor but I think I have cedar allergy.
	I was told so by a doctor.※

※When did you see a doctor and doctor told you that you have cedar allergy? Please write number below.

	When I was ( ) years old		( ) years ago

3. Have you ever told that you have allergic rhinitis other than cedar pollinosis?

	No
	Yes※

※If yes; please write the cause if you know it.

4. Have you ever had below mentioned allergies? Please mark ☑.

	allergic conjunctivitis		Food allergy
	hives		atopic dermatitis
	Oral Allergy Syndrome※		asthma

※Oral Allergy Syndrome: When you eat fruits and vegetables, you will feel itchy or uncomfortable in your mouth.

5. Have you ever had any diseases below or do you have any? Please mark ☑.

	sinusitis		angina
	hypertension		dyslipidemia
	diabetes mellitus		sleep apnea syndrome
	brain stroke		gastroesophageal regurgitation

6. How often do you have cold?

	5 times or more per year
	Less than 5 times a year

II. Asking other things.

1. Does your family have cedar pollinosis?

	no
	yes※

※If yes, who has one?

	father		mother		brother
	grandfather		grandmother		child

2. Does your family have any other allergic rhinitis other than cedar pollinosis?

	No
	Yes ※

※If yes, who it is?

	father		mother		brother
	grandfather		grandmother		child

3. Does your family have asthma?

	no
	yes※

※If yes, who it is?

	father		mother		brother
	grandfather		grandmother		child

4. Does your family have atopic dermatitis?

	no
	yes※

※If yes, who it is?

	father		mother		brother
	grandfather		grandmother		child

5. Does your family have allergic conjunctivitis?

	no
	yes※

※If yes, who it is?

	father		mother		brother
	grandfather		grandmother		child

6. Does your family have food allergy?

	no
	yes※

※If yes, who it is?

	father		mother		brother
	grandfather		grandmother		child

7. Does your family have aral allergy syndrome?

	no
	yes※

※If yes, who it is?

	father		mother		brother
	grandfather		grandmother		child

8. Do you smoke?

	no
	yes
	Not now, before

９． Does your family smoke in your house?

	no
	yes※

※If yes, who it is?

	father		mother		brother
	grandfather		grandmother		child
	partner		others		

１０． How many brothers and sisters do you have including yourself? Please write number. And please write in which order are you in your brothers and sisters?

	Numbers of brothers and sisters		I am the ( )th

１１． How many people do you live together including yourself? Please write number.

	persons

１２． Tell me about surroundings of your house

	suburb (residence area)
	village (surrounded by field, forest and nature)
	others

１３． While you are working or in a daytime, do you spend your time inside or outside?

	mainly inside
	mainly outside

１４． When you were a child, where were you playing around?

	often played outside
	seldom spend time outside

１５． Are you vulnerable to stress?

	Yes
	Not really.

１６． How many hours do you work a day? (if you work).

	hours

１７． How long is your average sleeping hours?

	hours

１８． Do you exercise more than 30 minutes a day for twice a week or more, and continue for more than a year?

	Yes
	No

１９． Do you have pets? Or have you had pets? Please mark☑.

	no	Yes I have now.	Not now but before I had
dog			
cat			
other（write what）			

２０． How often do you eat below mentioned items a week? Please mark ☑.

	seldom	1-2 a week	More than 3 times a week
Yogurt			
Meat			
Fish			
Fast food like burgers			
Beer			
Japanese sake			
Wine			
Soda			
Green tea, black tea, coffee			
Butter			
Egg			
Fruit			
Margarine			
Milk			
Nuts			
Noodles			
Bread			
Rice			
Potatoes			
Vegetables			
Bean product（Miso soup, tofu）			

This is the end of the interview. Thank you very much.