

Effects of Aging on the Natural History of Seasonal Allergic Rhinitis in Middle-Aged Subjects in South Chiba, Japan

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Key Words

Seasonal allergic rhinitis • Japanese cedar pollen •
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Abstract

Background: The natural history of allergic rhinitis has been examined in a few longitudinal studies. The purpose of the study was to investigate the course, development and remission of seasonal allergic rhinitis (SAR) over 10 successive years in middle-aged subjects. **Methods:** An annual questionnaire survey on allergic rhinitis symptoms combined with an examination of specific IgE has been undertaken in a rural town in south Chiba since 1995. The analyzed subjects were 703 residents who underwent every examination in 1995, 2004 and 2005. In the last 15 years, the annual pollen count in Chiba was highest in 2005. **Results:** The sensitization rates to cedar pollen decreased with age in the same subject groups over 10 years, but the prevalence of SAR was higher in 2005 compared with 1995. Of the 52 subjects with SAR in 1995, the symptoms had disappeared in 10 subjects in 2005. Specific IgE had converted to negative or borderline

in 4 of these patients, had decreased but was still positive in 4 and was increased or unchanged in 2. During the 10-year period, 22 subjects developed SAR, of whom 12 had increased specific IgE and 10 had similar or decreased specific IgE in 2005. **Conclusion:** SAR induced by cedar pollen takes a chronic course in the majority of middle-aged patients in south Chiba, Japan. The prevalence of SAR increased over 10 years due to a high level of pollen exposure. Changes in specific IgE were not directly associated with the development or remission of SAR.

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Introduction

Recent observations have suggested a significant worldwide increase in the prevalence of allergic rhinitis [1]. In Japan, Japanese cedar (*Cryptomeria japonica*) pollens are the major allergens. Since cedar forests cover nearly 18% of the total forest area of Japan [2], Japanese cedar produces enormous amounts of pollen that are dispersed over many kilometers and causes widespread sea-

sonal allergic rhinitis (SAR) induced by cedar pollen in major cities, including Tokyo [3]. The seasonal dispersion of cedar pollen normally starts in early February in the south Kanto area (Chiba and Tokyo), peaks from late February to March and ends in April [4].

The prevalence of SAR induced by cedar pollen has increased by more than 10% in the last 10 years based on questionnaire surveys [5–7]. However, findings based on only questionnaire data carry the risk of including many false-positive cases, as allergic rhinitis can be difficult to distinguish from acute upper respiratory infection and even healthy individuals may exhibit mild, nonspecific nasal symptoms such as sneezing and nasal secretion [8]. In addition, the cedar pollen season coincides with the winter season when upper respiratory infections are common, and an allergen-specific IgE test is necessary to avoid a high incidence of false positives. Moreover, sensitization to cedar pollen and the incidence of SAR induced by cedar pollen are influenced by variable seasonal pollen counts, especially for tree pollens. For example, dispersal of tree pollens such as Japanese cedar pollen has annual differences of more than 15-fold, in contrast to grass pollens [9]. The pollen-specific IgE titer also shows a seasonal change, and the sensitization and incidence rates of SAR induced by cedar pollen change every year [9, 10]. Thus, an accurate evaluation of the development, remission and natural course of SAR induced by cedar pollen is difficult.

Allergic rhinitis is a typical type 1 allergic disease, but the mechanisms of development and remission are complicated and have not been clarified yet. These are important fundamental phenomena that require understanding for the development of new treatment strategies for cure of the disease. In this study, we followed a population of middle-aged Japanese subjects in a typical small town in Japan for 10 years, including the years with the highest and lowest pollen counts during this period, to examine the course of allergic rhinitis.

Subjects and Methods

Subjects and Study Design

Maruyama-cho is a small rural town in the south of Chiba where movement of residents into the town is uncommon, and the town has been losing its population of children and young adults. We have determined the incidence of allergic rhinitis among the residents of Maruyama-cho annually since 1995. In 1995, we sent a letter to all residents of Maruyama-cho over 39 years of age ($n = 3,771$) to ask them to undergo a medical examination, and 1,560 subjects agreed to this request. The examination has subsequent-

ly been performed annually in the middle of June 2 months after the cedar pollen season. At the time of the examination the physicians checked the current nasal symptoms, history of allergic rhinitis and other allergic disease, and family history of allergic disease. Serum CAP-radioallergosorbent test (CAP-RAST; SRL Inc., Tokyo, Japan) scores for Japanese cedar pollen and mite (*Dermaphagoides pteronyssinus*) were also examined. Serum samples were frozen and all were analyzed within 2 days. We examined the changes of sensitization rates for Japanese cedar pollen and mite, and prevalence of SAR induced by cedar pollen and mite perennial allergic rhinitis over a 10-year period in the residents who had undergone every examination in 1995, 2004 and 2005.

The study was performed in compliance with the Ethical Guidelines for Clinical Studies and Good Clinical Practice and the Declaration of Helsinki (1989 and 2000 revisions). The protocol was approved by the Ethics Committee of Chiba University Hospital, and written informed consent was obtained from each subject prior to their participation in the study.

Pollen Counts

Pollen counts were determined with a Durham sampler (Nishiseiki Co., Funabashi, Japan) using the gravimetric method. In Japan, pollen counts are typically measured using the gravimetric method with a Durham sampler, in contrast to the typical use of a Burkard sampler in Western countries.

Diagnosis of Allergic Rhinitis

Mite perennial allergic rhinitis was defined as the presence of typical nasal symptoms almost all year around and a serum CAP-RAST score for mite of ≥ 2 . SAR induced by cedar pollen was defined as the presence of nasal symptoms in at least three successive pollen seasons since 1993, based on differences in annual pollen dispersal, and a serum CAP-RAST score for Japanese cedar pollen of ≥ 2 in 1995. The specific IgE level was classified using the following scores: 6, ≥ 100 UA/ml; 5, 50.0–99.9 UA/ml; 4, 17.5–49.9 UA/ml; 3, 3.50–17.4 UA/ml; 2, 0.70–3.49 UA/ml; 1, 0.35–0.69 UA/ml; 0, ≤ 0.34 UA/ml. A CAP-RAST score of 2–6 was regarded as positive, a score of 1 as borderline and a score of 0 as negative. The sensitization rates were calculated based on the number of subjects with a score of 2–6.

Remission and Development of SAR Induced by Cedar Pollen

Subjects who had SAR induced by cedar pollen in 1995 but did not have nasal symptoms in the cedar pollen season in 2005 (during which extremely high amounts of cedar pollen were scattered) were defined as in remission. In contrast, those who did not have nasal symptoms in 1995 but had both typical nasal symptoms and positive cedar-specific IgE in 2005 were defined as patients with newly developed SAR induced by cedar pollen.

Statistical Analysis

Comparison of the profiles of subjects was performed with two-tailed tests at a significance level of 5% using the χ^2 test in SAS v.8.02 (SAS Inc., Cary, N.C., USA). Sensitization rates, prevalence rates as well as the association between the background factors and the disappearance/development of symptoms were also analyzed by the χ^2 test.

Results

Profile of Subjects

The number of residents who underwent examinations in 1995, 2004 and 2005 was 703. The other 857 residents who dropped out of the study were older and had significantly lower rates for sensitization to Japanese cedar pollen and SAR induced by cedar pollen in 1995, compared to the subjects who were followed. There was no difference in gender between the two groups (table 1).

Pollen Counts

Dispersal of Japanese cedar pollen generally exhibits a bell-shaped pattern with time: cedar pollen dispersal starts in early February and reaches a peak between late February and early March, with some variation due to changes in the climate each year. The pollen dispersal season lasts for more than 8 weeks in the Chiba area.

The annual counts of cedar pollen (the total of daily counts from February to April) were 4,600, 500 and 7,850 grains/cm²/season in 1995, 2004 and 2005, respectively. The average annual pollen count was 3,000 grains/cm²/season over the 15 years since the start of the pollen count survey in Chiba, and was lowest in 2004 and highest in 2005.

Sensitization Rates for Japanese Cedar Pollen and Prevalence of SAR Induced by Cedar Pollen

Sensitization rates for Japanese cedar pollen in males are shown in figure 1a. Changes of sensitization rate in the same subjects from 1995 to 2005 are shown by arrows in the figure: these rates decreased over a 10-year period by 1.7% (1/59), 5.1% (4/79) and 12.7% (15/118) in their 40s, 50s and 60s, respectively, in 1995. The decrease was significantly greater in the 60s age group compared to the 40s or 50s age groups. Sensitization rates for Japanese cedar pollen in females are shown in figure 1b. These rates decreased by 1.8% (2/112) and 6.5% (9/139) from 1995 to 2005 in their 40s and 50s, respectively, in 1995, with a significantly greater decrease in the 50s age group.

The prevalence of SAR induced by cedar pollen in 2004 slightly decreased compared with 1995 in males in their 40s and 60s in 1995 (fig. 2a). However, the prevalence increased in 2005 compared with 1995, except for subjects in their 60s in 1995. The changes in rates from 1995 to 2005 were 5.1% (3/59) and 6.3% (5/79) in their 40s and 50s, respectively, in 1995, with no significant difference between these changes. The prevalence in females is shown in figure 2b, and an increased prevalence over a 10-year period was found in their 40s and 60s in 1995.

Table 1. Profile of subjects in 1995

	Followed in 2005 (n = 703)	Dropped out in 2005 (n = 857)
Age in 1995, %		
40s	24.3	14.9
50s	31.0	15.1
60s	36.7	35.0
70s	8.0	35.0
p value	<0.001 (70s vs. total of others)	
Gender, %		
Female	59.5	57.8
Male	40.5	42.2
p value	0.50	
Sensitization to cedar pollen, %		
Positive	22.0	16.5
Negative or borderline	78.0	73.5
p value	<0.01	
Diagnosis of SAR induced by cedar pollen, %		
Yes	7.4	4.3
No	92.6	95.7
p value	<0.01	
Sensitization to mite, %		
Positive	18.3	14.6
Negative or borderline	81.7	85.4
p value	<0.05	
Diagnosis of mite perennial allergic rhinitis, %		
Yes	1.8	1.3
No	98.2	98.7
p value	0.37	

The prevalence was similar in 1995 and 2004. The changes in rates from 1995 to 2005 were 4.5% (5/112) and 1.4% (2/140) in their 40s and 60s, respectively, in 1995, with no significant difference between these changes.

Table 2 shows changes in age-specific sensitization rates for Japanese cedar pollen and prevalence rates of SAR in all subjects over a 10-year period. The sensitization rate among the 50s age group in 2005 was significantly greater than that among the 50s age group in 1995. The prevalence rates of SAR among the 50s and 60s age groups in 2005 were significantly greater than those among the 50s and 60s age groups in 1995.

Sensitization Rates for Mite and Prevalence of Mite Perennial Allergic Rhinitis

Sensitization rates for mite in males decreased with age, and the changes in sensitization from 1995 to 2005 were 6.8% (4/59), 10.1% (8/79) and 11.9% (14/118) in males in their 40s, 50s and 60s, respectively, in 1995, with no

Fig. 1. Sensitization rates for Japanese cedar pollen. The changes in sensitization in the same subjects from 1995 to 2005 are shown by arrows. The rates decreased over a 10-year period in most groups except for males in their 70s (**a**) and in females in their 60s (**b**) in 1995.

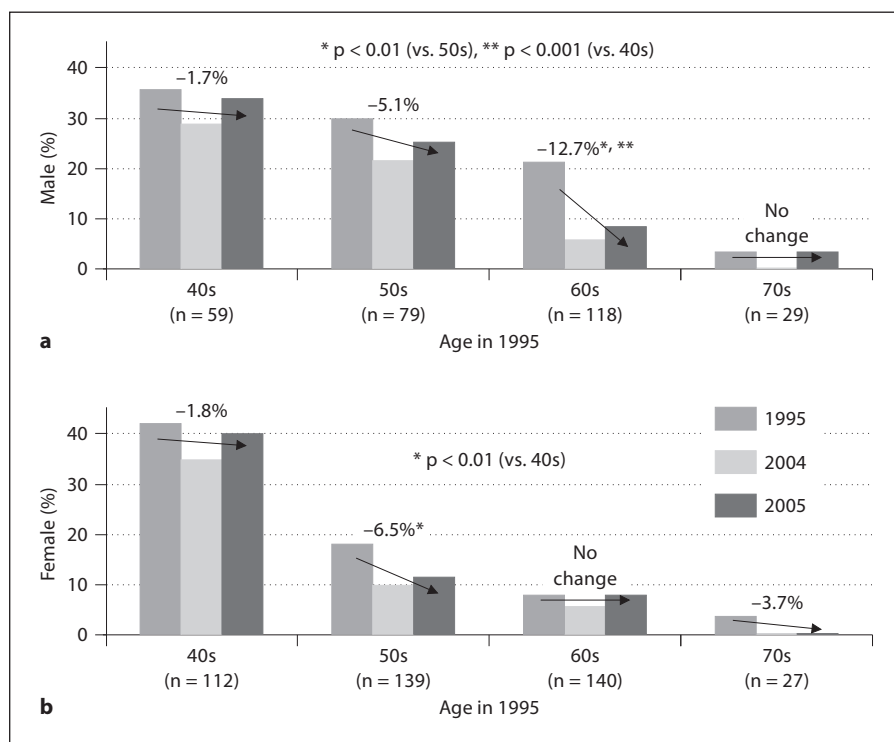


Fig. 2. Prevalence of SAR induced by Japanese cedar pollen. The changes in prevalence in the same subjects from 1995 to 2005 are shown by arrows. The prevalence increased over a 10-year period in most groups except for males in their 60s (**a**) and females in their 50s (**b**) in 1995.

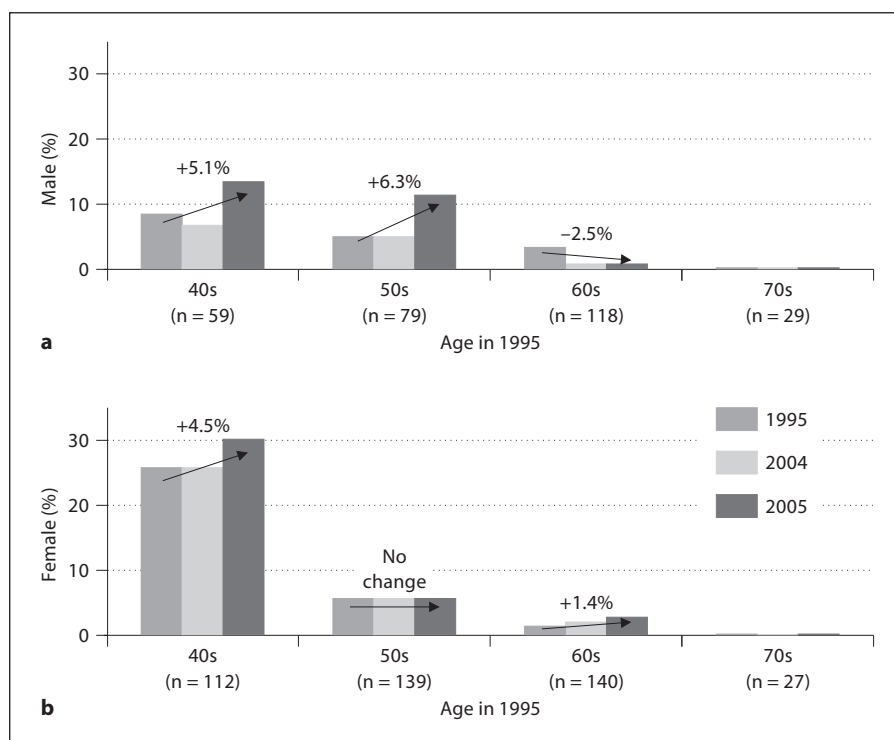


Table 2. Changes in age-specific sensitization rates for Japanese cedar pollen and prevalence rates of SAR in all subjects over a 10-year period

Age	Sensitization rates for Japanese cedar pollen, %			Prevalence rates of SAR, %		
	1995	2005	p value	1995	2005	p value
40s	39.8	–	–	19.9	–	–
50s	22.5	38.0	$<1.0 \times 10^{-3}$	5.5	24.6	$<1.0 \times 10^{-7}$
60s	14.0	16.5	0.44	2.3	7.8	<0.01
70s	3.6	8.1	0.36	0	1.9	0.64
80s	–	1.8	–	–	0	–

significant differences among the data. Sensitization rates for mite in females also decreased with age, and the decreases from 1995 to 2005 were 8.9% (10/112) and 11.5% (16/139) in females in their 40s and 50s, respectively, in 1995, with a significantly greater decrease in the 50s age group (data not shown).

The prevalence of mite perennial allergic rhinitis was low in males and females ($<7\%$). The prevalence decreased with age in all groups and was unaffected by the annual pollen count (data not shown).

Remission of Symptoms of SAR Induced by Cedar Pollen

Among the 703 subjects, 52 had been diagnosed with SAR induced by cedar pollen in 1995. The disease had not resolved in 42 (80.8%) of these patients, but 10 (19.2%) did not have symptoms of SAR induced by cedar pollen in 2005, a year in which there was an extremely high pollen count (table 3). These 10 subjects continued to have no nasal symptoms in pollen seasons 2006 and 2007 (data not shown). Older and male patients showed a tendency for more chance of remission, but there was no correlation with the age at onset of SAR induced by cedar pollen, other allergic diseases or family history of SAR induced by cedar pollen. Cedar-specific IgE levels were higher in patients without remission than in those with remission. However, the cedar-specific IgE of each subject changed to negative or borderline in 4, decreased but was still positive in 4 and increased or was unchanged in 2 of the 10 subjects with remission (fig. 3).

Development of SAR Induced by Cedar Pollen

Among the 703 subjects, 651 did not have symptoms of SAR induced by cedar pollen in 1995. Of these subjects, 629 had not developed SAR induced by cedar pollen in

Table 3. Association between the background factors and the disappearance of symptoms in subjects with SAR induced by cedar pollen in 1995

	Symptoms disappeared in 2005 % (n = 10)	Symptoms continued in 2005 % (n = 42)
Age in 1995		
40s	30.0	73.8
50s	40.0	19.0
60s	30.0	7.2
p value	<0.05	
Gender		
Female	40.0	83.3
Male	60.0	16.7
p value	<0.05	
Cedar-specific IgE		
CAP-RAST 2–3	80.0	33.3
CAP-RAST 4–6	20.0	66.7
p value	<0.05	
Mite-specific IgE		
CAP-RAST <2	50.0	61.9
CAP-RAST ≥ 2	50.0	38.1
p value	0.74	
Age at the onset, years		
<40	40.0	57.1
≥ 40	60.0	42.9
p value	0.53	
Other allergic disorders ¹		
With disorders	20.0	11.9
Without disorders	80.0	88.1
p value	0.87	
Family histories of SAR induced by cedar pollen ²		
With family histories	10.0	11.9
Without family histories	90.0	88.1
p value	0.70	

¹ Other allergic disorders: mite perennial allergic rhinitis, bronchial asthma and atopic dermatitis.

² Histories of parents, brothers, and sisters.

2005, but 22 (3.4%) had developed the disease over 10 years (table 4). Younger subjects showed a tendency for more chance of development. There was no difference between genders. Cedar-specific IgE levels in 1995 were higher in patients who developed the disease compared to those without disease development. Among the 703 subjects, 103 were sensitive to Japanese cedar pollen, but did not have any symptoms of SAR induced by cedar pollen in 1995. Of these 103 subjects, 17 (16.5%) had symptoms of SAR induced by cedar pollen in 2005. The cedar pollen-specific IgE increased in 7, decreased in 8 and was unchanged in 2 of the 17 subjects with development of the

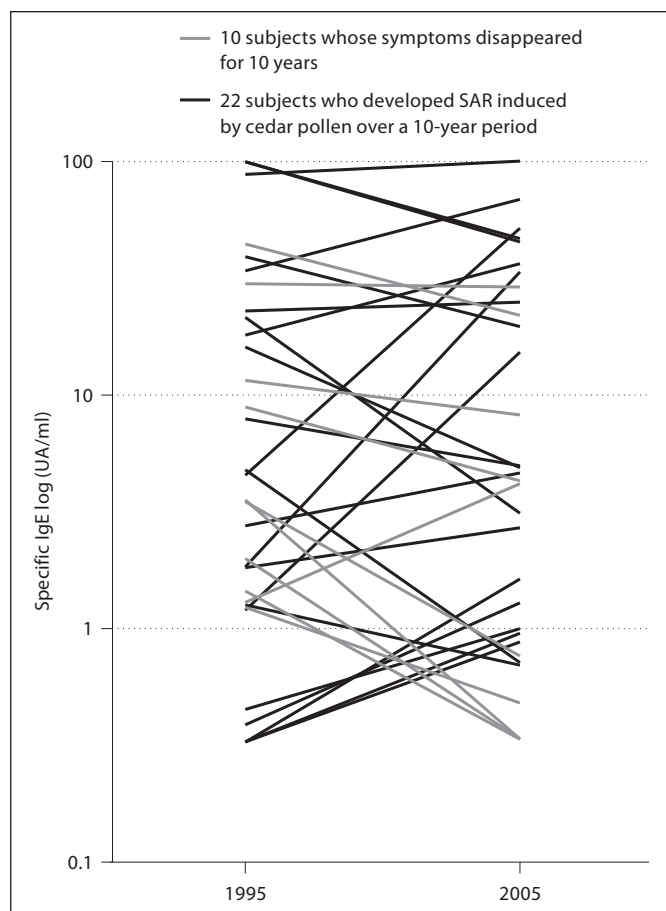


Fig. 3. Changes of specific IgE titer to Japanese cedar pollen. The changes of cedar pollen-specific IgE did not have a constant tendency. Changes in specific IgE were not directly associated with development or remission of SAR.

disease (fig. 3). Five of the 548 (0.9%) subjects who were not sensitive to cedar pollen in 1995 were sensitized and had symptoms of SAR induced by cedar pollen in the 2005 pollen season. Eighteen of the 22 patients with newly developed SAR induced by cedar pollen continued to have symptoms during the pollen seasons in 2006 and 2007, when the pollen counts were low.

Discussion

This study provides a longitudinal analysis of the same middle-aged subjects for 10 years, including comparisons among seasons with large differences in cedar pollen counts: the highest in 2005 and lowest in 2004 over the last 15 years. The number of subjects in the study was

Table 4. Association between the background factors and the development of symptoms in subjects without SAR induced by cedar pollen in 1995

	With SAR in 2005, % (n = 22)	Without SAR in 2005, % (n = 629)
Age in 1995		
40s	50.0	20.0
50s	40.9	31.3
60s	9.1	39.8
70s	0	8.9
p value	<0.001	
Gender		
Female	54.5	58.3
Male	45.5	41.7
p value	0.72	
Cedar-specific IgE		
CAP-RAST<2	22.7	86.3
CAP-RAST 2–3	40.9	13.5
CAP-RAST 4–6	36.4	0.2
p value	<0.001	
Mite-specific IgE		
CAP-RAST<2	50.0	84.6
CAP-RAST≥2	50.0	15.4
p value	<0.001	
Other allergic disorders ¹		
With disorders	0	4.0
Without disorders	100	96.0
p value	0.69	
Family histories of SAR induced by cedar pollen ²		
With family histories	4.5	3.5
Without family histories	95.5	96.5
p value	0.74	

¹ Other allergic disorders: mite perennial allergic rhinitis, bronchial asthma, and atopic dermatitis.

² Histories of parents, brothers, and sisters.

limited and the gender and age distributions indicate that the population is not representative of the national middle-aged Japanese population. However, the subjects who dropped out of the study included more nonsensitized subjects without allergic rhinitis who were older than 70 years of age in 1995. Therefore, we believe that the longitudinal epidemiological survey of allergic rhinitis in the same middle-aged subjects combined with an examination of specific IgE and annual pollen counts provides new information on the current status of allergic rhinitis, since very few such surveys have been performed.

A decreased sensitization and prevalence to cedar pollen and mite were observed in the middle-aged subjects

in this study, as also reported in other countries [11–13]. There also seemed to be a difference between genders, with reduced sensitization occurring about 10 years earlier in females. However, with exposure to a high pollen level, sensitization to cedar pollen and the prevalence of SAR induced by cedar pollen increased in subjects in their 50s to 70s regardless of gender. The annual pollen count in 2005 (7,850 grains/cm²/season) was about 2.5 times higher than the mean over the last 15 years. Subjects with low cedar pollen-specific IgE levels (CAP-RAST scores of 2–3) tended to contribute to the decrease in sensitization, whereas subjects with high specific IgE levels tended to have symptoms under exposure to a high level of cedar pollen.

Genetic and environmental factors are involved in the onset of allergic rhinitis, as with many other diseases [14, 15]. The relevance of genetic factors cannot be ignored, but environmental factors may also have played a major role in the recent increase in allergic diseases. In Japan, after World War II, an extensive afforestation program was initiated using Japanese cedar because of its fast growth and its value as a building material. Consequently, however, the amount of airborne Japanese cedar pollen has increased dramatically after the 1970s [16]. Pollen dispersal varies from year to year, but annual pollen counts have shown a tendency to increase with time and are a major environmental factor in allergic rhinitis [17]. There are other environmental factors which can change the predisposition to produce IgE and may also have contributed to the increase in allergic rhinitis. However, increased pollen dispersal probably has a major role in the increased prevalence of SAR induced by cedar pollen in middle-aged subjects, since sensitization to mite and the prevalence of mite perennial allergic rhinitis decreased with age in the current study.

Remission or development of allergic rhinitis has only been examined in a few longitudinal studies [9, 18–20] and evaluation of these processes is particularly difficult in SAR induced by tree pollens, as described above. During the 10 years of the present study, remission and development of SAR induced by cedar pollen occurred in 19.2% (10/52) and 3.4% (22/651) of the middle-aged subjects, respectively. Mite-allergic rhinitis remitted in 8 of 13 subjects (61.5%) and did not newly develop in any subjects (data not shown). SAR took a chronic course in the majority of middle-aged patients in the current study. Younger subjects showed a tendency for more risk of development of SAR induced by cedar pollen and less chance of remission, but the change in the pollen-specific IgE level in each individual was not directly associated

with remission or development. These data showed no differences between genders.

There was a high rate of asymptomatic sensitization in this study. 103 subjects were sensitized without symptoms at baseline, and of these only 17 developed symptoms during the follow-up period. One of the reasons of this high rate of asymptomatic sensitization is low CAP-RAST scores of the 103 subjects. Among the 103 subjects, 94 (91.3%) showed scores of 2–3. The sensitization rates were calculated based on the number of subjects with a CAP-RAST score of 2–6. We did not perform skin tests. Skin prick test might be more sensitive and show a higher correlation with allergic symptoms; however, CAP-RAST test allowed a quantitative analysis. In this study, high CAP-RAST scores could be a predictive factor for the new development of SAR (table 4). The cross-reactivity to carbohydrate determinants may cause false-positive specific IgE determinations as reported in some pollens in vitro [21–24]; however, the cross-reactivity of specific IgE to carbohydrate determinants in cedar pollen has not been clarified yet.

Overall, this study suggests that SAR induced by cedar pollen does not resolve in the majority of middle-aged patients over a 10-year period and takes a chronic course. The prevalence of mite-allergic rhinitis has remained low and decreased since 1995, but that of SAR induced by cedar pollen has increased in middle-aged subjects in south Chiba, Japan. This increase is associated with the rise of cedar pollen dispersal. Remission and development of SAR induced by cedar pollen were both observed in middle-aged subjects over a 10-year period, and were not directly associated with the change in the specific IgE level in each subject. Further studies are required to clarify the basis of these observations.

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