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Original Article

Comparison of sensitization and prevalence of Japanese cedar pollen and mite-induced perennial allergic rhinitis between 2006 and 2016 in hospital workers in Japan

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AR	allergic rhinitis
SAR	seasonal allergic rhinitis
PAR	perennial allergic rhinitis
JC	Japanese cedar
IgE	Immunoglobulin E

ABSTRACT

Background: The prevalence of allergic rhinitis (AR) is increasing worldwide, mainly due to an increase in antigen exposure. We conducted an epidemiological study involving the staff of the University of Fukui Hospital and its associated hospital in 2006. There were 1540 participants aged ≥ 20 years, and the rates of Japanese cedar (JC) pollinosis and mite-induced perennial allergic rhinitis (PAR) were 36.8% and 15.8%, respectively. In 2016, we conducted a second survey.

Methods: The rate of sensitization to JC pollen and mites and the prevalence of JC pollinosis and mite-induced PAR were analyzed based on data from questionnaires and antigen-specific immunoglobulin E (IgE) levels.

Results: In the present study, we analyzed data of 1472 participants aged between 20 and 59 years. Total sensitization to JC pollen and total prevalence of JC pollinosis were 57.8% (851/1472) and 40.8% (601/1472), respectively. Total sensitization to mites and total prevalence of mite-induced PAR were 41.4% (610/1472) and 18.8% (276/1472), respectively. Total prevalence of JC pollinosis and mite-induced PAR increased significantly over a decade. Among the 334 people who participated in the 2006 and 2016 cross-sectional studies, 13% of JC pollinosis and 36% of mite-induced PAR experienced remission. However, since the number of new onset cases was higher than the number of remission cases, a slight increase in prevalence was observed over a decade.

Conclusions: The prevalence of JC pollinosis and mite-induced PAR continues to show increasing trends, accompanied by an increase in antigen exposure. The remission rate of JC pollinosis was particularly low.

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Introduction

An increase in antigen exposure is thought to be one of the causes of the rise in allergic diseases, and an increase in JC pollinosis has been attributed to domestic circumstances, such as the

Japanese government's policy of planting cedar forests.^{1,2} After World War II, approximately 18% of Japan's land mass was planted with cedar forests to secure timber for building homes, increasing exposure to antigens. Sample surveys with antigen-specific IgE tests conducted in Tokyo every 10 years showed a marked increase in the prevalence of JC pollinosis, from 10.0% in 1986 to 19.4% in 1996, and from 28.2% in 2006 to 45.6% in 2016.³ An epidemiological study by Urashima *et al.* showed that people born after 1973 were at a higher risk of developing JC pollinosis than those born earlier.⁴ The study suggests that increased exposure to pollen in early ages, possibly due to tree plantation, leads to early development of JC pollinosis. Sasaki *et al.* carried out a nationwide cross-sectional

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investigation based on the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire. Almost 48,000 and 36,000 participants aged 13–15 years took part in this study in 2005 and 2015, respectively. An increase was not seen in the incidence of wheezing (8.7%–8.2%) and eczema (9.9%–9.7%), but the prevalence of rhino-conjunctivitis increased from 20.5% to 26.7%.⁵ They concluded that this increase in the prevalence of rhino-conjunctivitis was due to the rapid increase in JC pollinosis. In a report on indoor mite contamination, measurements of mite allergens in bedding showed higher levels of mite antigens (Der 1) in Japan when compared to the United States and Europe.^{6–10} Global warming is thought to be one of the causes for the increase in allergic diseases caused by mites.¹¹ It has also been reported that when people spend more time indoors due to high outdoor temperatures, the use of air conditioning leads to increased exposure to mites.

Nakamura *et al.* conducted a nationwide, cross-sectional, questionnaire-based study of otolaryngologists and their families in 1998 and 2008, analyzing 17,301 and 15,673 participants, respectively. The study found that the mean prevalence among all age groups rose from 16.2% to 26.5% for JC pollinosis and from 18.7% to 23.4% for PAR.¹² In 2001, Okuda conducted a questionnaire survey addressing the general population and reported a 19.4% prevalence of JC pollinosis.¹³ Two other surveys performed around the same time obtained similar figures and suggested an increase in prevalence in younger age groups. Osawa *et al.* conducted an epidemiological survey of children aged 18 months.¹⁴ Of the 408 subjects, 44 (10.7%) tested positive for JC pollen-, mite-, or cat antigen-specific IgE, suggesting that sensitization had already occurred at 18 months after birth. A cross-sectional study involving 19,461 high-school students aged 15–18 years conducted by Tokunaga *et al.* reported an AR prevalence rate of 19.2% in 2012.¹⁵ Taken together these datasets suggest that 18 months is too early, but at 15–18 years of age AR prevalence can already be considered.

Yonekura *et al.* started a cohort study in 1995 to observe the general population of Japanese individuals in their 40s for 10 years.² The results of the questionnaire survey on AR symptoms and measurements of antigen-specific IgE showed that 10 of the 52 JC pollinosis patients (19.2%) were in remission 10 years later. New-onset cases of JC pollinosis occurred in 3.4% (22/629) of the participants with a few new cases occurring from the age of 40 years onward. Furthermore, remission was observed in 61.5% (8/13) of mite-induced PAR cases, and no new cases occurred. These results suggest that few new cases of JC pollinosis and mite-induced PAR occur once people enter their 40s.

In 2006, we recruited members of the staff from the University of Fukui Hospital and associated hospitals for the study.¹⁶ The overall prevalence of AR was 44.2%. We conducted the second survey with 1472 participants in 2016 and compared the results of these 2 cross-sectional studies analyzing rates of spontaneous remission of AR in a cohort of 334 people who participated in both studies.

Methods

Survey subjects

The 2016 survey recruited participants from the staff of the University of Fukui and Tannan Regional Medical Center, which included medical doctors, nurses, co-medical staff, office workers, and academic staff. The region experiences snowfall in winter, which means that the JC pollen season begins in late February in most years and peaks in mid-March. The amount of pollen then decreases throughout April, with the season ending in early May. The amount of dispersed JCP was measured using a Durham pollen

collector that was set up in an open space at the University of Fukui. The total daily pollen count was expressed as the number of pollen particles per square centimeter.¹⁷ The observation period of the pollen count was from February 1 to April 30, 2016. The JC pollen levels in Fukui were 3356 and 605 pollen grains/cm² in 2005, 2006, and 3170, 1870, 2136, and 4545 from 2015 to 2018, respectively.

We conducted a survey and recruited participants at the University of Fukui in June 2006 and June 2016, and at Tannan Regional Medical Center in September 2006 and September 2016. The survey in 2006 did not consider JC pollen forecast, and the second survey was carried out 10 years later, in 2016. Blood samples and questionnaires were obtained from the participants after they provided informed consent. They were asked if they had any nasal symptoms for more than two consecutive JC pollen seasons or perennial periods. Participants who had undergone immunotherapy were excluded. This study was planned and conducted in accordance with the Declaration of Helsinki and medical ethical guidelines on human subjects. The participants provided written informed consent, and patient anonymity was preserved using methods approved by the Ethics Committee of the University of Fukui Hospital (approval number: 20150128).

Antigen-specific IgE measurement

The diagnosis of AR was based on the combination of a serum-specific IgE score of ≥ 2 and the presence of nasal symptoms such as sneezing, nasal discharge, or nasal congestion.¹² Blood samples were evaluated for 10 varieties of serum-specific IgE: *Cryptomeria japonica*, *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Dactylis glomerata*, *Chamaecyparis obtusa*, *Alnus japonica*, *Betula platyphylla* var. *japonica*, *Ambrosia artemisiifolia*, *Candida*, and *Aspergillus*. The Phadia ImmunoCAP (LSI Medience Corporation, Japan) was used for the measurements, and clinical assessments were made by scoring the IgE antibody concentration (UA/ML).¹² For sensitization, a score of 0 (≤ 0.34) was considered negative, 1 (0.35–0.69) was considered false positive, and ≥ 2 (≥ 0.70) was positive.

Participants in the 2016 cross-sectional study were divided into 2 groups for analysis of their health complications and life history. Participants who tested positive for any serum IgE antibody and had seasonal or perennial rhinitis symptoms were categorized into the AR group. Participants who were positive for any serum IgE antibody but did not have seasonal or perennial rhinitis symptoms were categorized into the non-AR group. Those who had seasonal or perennial rhinitis symptoms but were negative for serum IgE antibodies were also categorized into the non-AR group.

Statistical analysis

Fisher's exact test and the chi-square test were used to compare the AR and non-AR groups in the 2016 survey. The differences between the 2006 and 2016 sensitization rates for JC pollen and mites and the prevalence rates for AR were also compared using the chi-square test. Wilcoxon matched-pairs signed-rank tests were used to compare changes in IgE levels between 2006 and 2016 in the JC pollinosis and mite-induced AR remission and new development groups.

Results

Summary of participants

The participants were 1411 University of Fukui staff members and 87 Tannan Regional Medical Center staff members. Twenty-six people aged ≥ 60 years were excluded because the number of

participants in this age group was smaller than in the other age groups. Finally, data from 1472 people were analyzed (Table 1); the mean age was 38.4 years, with 338 men (23%). The participants were 767 nurses, 257 medical doctors, 201 office workers, 191 co-medical staff, and 56 academic staff. Regarding complications, 9.6% had bronchial asthma, 16.7% had atopic dermatitis, 11.5% had allergic conjunctivitis, and 6.4% had food allergies.

Sensitization rates for airborne antigens

C. japonica sensitization was observed in 57.8% of the subjects and this was the highest rate among inhalant antigens that we examined (Table 2). Participants in their 20s and 30s in 2016 had higher rates for JC pollen sensitization (65.3% and 63.3%, respectively), while those in their 40s and 50s had the lower rates of (48.1% and 51.2%, respectively). The second highest sensitization rate was reported for *D. farinae*, accounting for 40.7% of the participants. Sensitization to *D. farinae* was high among participants in their 20s and 30s (47.3% and 48.6%, respectively), but was low among those in their 40s and 50s (40.2% and 21.2%, respectively). The results for *D. pteronyssinus* were similar to those for *D. farinae*. The third highest sensitization rate was reported for *D. glomerata*

(25.0%), followed by *C. obtusa* (19.1%), *B. platyphylla* var. *japonica* (9.8%), *A. japonica* (9.4%), and *A. artemisiifolia*, *Candida*, and *Aspergillus* ($\leq 5\%$). Sensitization to any kind of antigen was observed in 70.2% (1034/1472) of the participants (Fig. 1). Of these individuals, 26.4% (389/1472) were sensitized only to JC, 31.4% (462/1472) to JC and mites, 10.3% (151/1472) only to mites, and 2.2% (32/1472) to antigens other than JC and mites. Overall, the JC and mites were the primary allergens for AR.

Comorbid allergic diseases in the AR group

Asthma was significantly more common in the AR group (13.7%) (Table 3). Rates of atopic dermatitis (19.9%), allergic conjunctivitis (18.0%), and food allergies (7.8%) were also higher in the AR group than in the non-AR group. No significant differences were observed in smoking history, frequency of influenza vaccinations, number of siblings, or position among siblings.

Prevalence of JC pollen sensitization and JC pollinosis over 10 years

In the present study, total sensitization to JC pollen and total prevalence of JC pollinosis in 2016 were 57.8% (851/1472) and 40.8%

Table 1

Participant characteristics in a cross-sectional study conducted at the University of Fukui and Tannan Regional Medical Center in 2016.

Age range (years)	Number [†]	Sex	Number	Comorbid allergic disease				
				Asthma [‡]	Atopic dermatitis	Allergic conjunctivitis	Food allergy	None
20–29	406	Men	71	14	15	6	3	40
		Women	335	41	75	28	28	191
30–39	430	Men	101	12	32	17	12	108
		Women	329	31	61	43	19	205
40–49	342	Men	85	6	12	6	5	61
		Women	257	19	33	33	13	154
50–59	294	Men	81	5	4	5	2	63
		Women	213	14	14	32	12	144
Total	1472	Men	338	37	63	34	22	272
		Women	1134	105	183	136	72	694

[†] There were 1472 participants aged 20–59 years.

[‡] The number of participants with allergic disease complications.

Table 2

Measurements of 10 types of antigen-specific IgE in the 2016 cross-sectional study of 1472 people.

		20–29 (n = 406)	30–39 (n = 430)	40–49 (n = 342)	50–59 (n = 294)	Total	%
<i>Cryptomeria japonica</i>	N [†]	265	272	164	150	851	57.8
	%	65.3	63.3	48.1	51.2		
<i>Dermatophagoides farinae</i>	N	192	209	137	62	600	40.7
	%	47.3	48.6	40.2	21.2		
<i>Dermatophagoides pteronyssinus</i>	N	186	210	135	56	587	39.9
	%	45.8	48.8	39.6	19.1		
<i>Dactylis glomerata</i>	N	138	118	66	46	368	25.0
	%	34.0	27.4	19.4	15.7		
<i>Chamaecyparis obtusa</i>	N	101	83	59	38	281	19.1
	%	24.9	19.3	17.3	13.0		
<i>Betula platyphylla</i>	N	56	44	25	19	144	9.8
	%	13.8	10.2	7.3	6.5		
<i>Alnus japonica</i>	N	56	42	25	16	139	9.4
	%	13.8	9.8	7.3	5.5		
<i>Candida albicans</i>	N	23	20	17	11	71	4.8
	%	5.7	4.7	5.0	3.8		
<i>Ambrosia artemisiifolia</i>	N	20	11	15	6	52	3.5
	%	4.9	2.6	4.4	2.0		
<i>Aspergillus fumigatus</i>	N	5	3	6	2	16	1.1
	%	1.2	0.7	1.8	0.7		

[†] Positive number of antigen-specific IgE using the Phadia ImmunoCAP. IgE values ≥ 0.70 (scores ≥ 2) were considered positive. IgE, Immunoglobulin E.

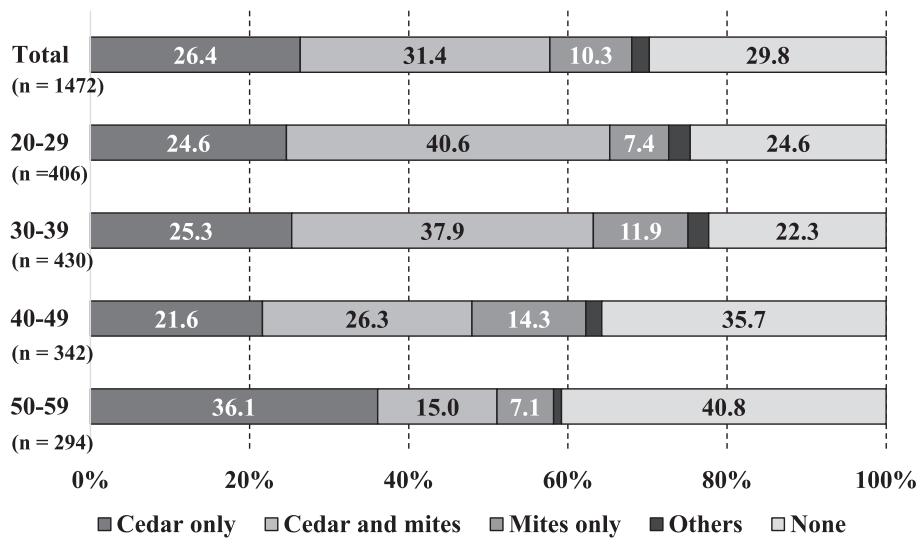


Fig. 1. Overlapping specific antigen positivity. The percentage of participants from the 2016 study who were ImmunoCAP positive. There were five groups categorized as Cedar only: positive only for cedar pollen, Cedar and mites: positive for cedar pollen and mites, Mites only: positive only for mites, Others: positive for any of *Dactylis glomerata*, *Chamaecyparis obtusa*, *Alnus japonica*, *Betula platyphylla* var. *japonica*, *Ambrosia artemisiifolia*, *Candida*, and *Aspergillus*, but negative for both of JC pollen and mites, and None: negative for all antigens.

(601/1472), respectively, (Table 4A, B). Total prevalence increased significantly over a decade ($p = 0.022$). Based on the results of the 2 cross-sectional studies, we compared changes in sensitization rates over a decade, for example, those in their 20s in 2006 and then the

Table 3
Comparison of AR with complications and life history.

	Allergic rhinitis [†] (n = 715)	Non-allergic rhinitis [‡] (n = 757)	p value
Comorbidity with asthma			
Yes	95 (13.7%)	48 (6.6%)	<0.01**
No	597 (86.3%)	683 (93.4%)	
Comorbidity with other allergic disease			
Atopic dermatitis	145 (19.9%)	90 (12.9%)	<0.01**
Allergic conjunctivitis	131 (18.0%)	34 (4.9%)	
Food allergy	57 (7.8%)	31 (4.4%)	
None	396 (54.3%)	545 (77.9%)	
Smoking history			
Current smoking	45 (6.3%)	47 (6.4%)	NS
Past smoking	101 (14.0%)	107 (14.6%)	
Never	573 (79.7%)	580 (79.0%)	
Influenza vaccine			
Every year	662 (91.6%)	680 (89.0%)	0.061
Occasionally	51 (7.1%)	60 (7.9%)	
Never	10 (1.4%)	24 (3.1%)	
Number of siblings			
1	43 (6.0%)	38 (5.0%)	NS
2	387 (54.1%)	374 (49.7%)	
3	258 (36.1%)	290 (38.5%)	
4	30 (4.2%)	46 (6.1%)	
5	4 (0.6%)	4 (0.5%)	
6	0 (0.0%)	1 (0.1%)	
Position among siblings			
1st	369 (51%)	364 (48.4%)	NS
2nd	268 (37.1%)	266 (35.4%)	
3rd	77 (10.7%)	112 (14.9%)	
4th	6 (0.8%)	9 (1.2%)	
5th	3 (0.4%)	1 (0.1%)	

Participants in the 2016 cross-sectional study were divided into 2 groups.

[†] Allergic rhinitis group, which showed positivity for serum IgE antibody and had seasonal or perennial rhinitis.

[‡] Non-allergic rhinitis group, which had no seasonal or perennial rhinitis symptoms even if there was positivity for serum IgE antibodies.

** $p < 0.01$.

IgE, Immunoglobulin E.

same group in their 30s in 2016. However, we did not compare age groups, such as participants in their 20s in 2006 with participants in their 20s in 2016. In this comparison, participants in their 20s in 2006, born between 1977 and 1986, showed 59.2% of sensitization to JC pollen. This group reached their 30s in 2016 with 63.3% sensitization, however this increase was not statistically significant (Table 4A). Participants in their 30s in 2006, born in 1967–1976, showed 51.9% sensitization, and little change (48.0%) when they reached their 40s in 2016. Participants in their 40s in 2006, born in 1957–1966, showed no sensitization change compared to their 50s in 2016. Although participants who were in their 20s in 2016, born between 1987 and 1996, did not have results from the 2006 survey, they showed 65.3% of sensitization, a rate as high as that of participants in their 30s in 1977–1986, indicating increased sensitization over a decade.

The prevalence of JC pollinosis in participants in their 20s in 2006, born in 1977–1986, showed a significant change from 35.2% to 43.7% when participants reached their 30s in 2016 (Table 4B). Participants who were born in 1967–1976 and 1957–1966 showed no changes. Although participants in their 20s in 2016, born in 1987–1996, did not have results from the 2006 survey to be compared with, they showed a 43.3% prevalence that was as high as that from participants in their 30s in 2016. This result suggests that JC pollinosis is induced at 10 years of age or younger. The participants were questioned about the onset age of JC pollinosis. Among participants in their 20s with JC pollinosis in 2016, 51% answered that JC pollinosis initiated between 10 and 19 years of age (data not shown).

Prevalence of sensitization to mites and mite-induced PAR over 10 years

In the present study, total sensitization to mites and total prevalence of mite-induced PAR were 41.4% (610/1472) and 18.8% (276/1472), respectively (Table 4C, D). Total prevalence increased significantly over a decade ($p = 0.035$). Sensitization to mites for participants their 20s in 2006, born in 1977–1986, showed minimal change (48.5%–49.8%) when they reached their 30s in 2016 (Table 4C). Furthermore, participants in their 30s in 2006, born in 1967–1976, and in their 40s in 2006, born in 1957–1966, did not

Table 4

Sensitization to JC pollen and mites and prevalence of allergic rhinitis in 2006 and 2016 among each birth year cluster group.

A Sensitization for Japanese cedar pollen							
Birth year of participants	2006			2016			p [§] value
	Age in 2006	Positive number [†]	Percentage [‡] (95% CI)	Age in 2016	Positive number	Percentage (95% CI)	
1957–1966	40s	208/394	52.8 (47.9–57.7)	50s	150/294	51.0 (45.3–56.7)	0.64
1967–1976	30s	226/435	51.9 (47.3–56.6)	40s	164/342	48.0 (42.7–53.2)	0.27
1977–1986	20s	421/711	59.2 (55.6–62.8)	30s	272/430	63.3 (58.7–67.8)	0.18
1987–1996	(10s)	–	–	20s	265/406	65.3 (60.7–69.9)	–
Total		855/1540	55.5 (53.0–58.0)		851/1472	57.8 (55.3–60.3)	0.2
B Prevalence of allergic rhinitis for JCP							
Birth year of participants	2006			2016			p value
	Age in 2006	Positive number	Percentage (95% CI)	Age in 2016	Positive number	Percentage (95% CI)	
1957–1966	40s	156/394	39.6 (34.8–44.4)	50s	117/294	39.8 (34.2–45.4)	0.95
1967–1976	30s	160/435	36.8 (32.3–41.3)	40s	120/342	35.1 (30.1–40.1)	0.62
1977–1986	20s	250/711	35.2 (31.7–38.7)	30s	188/430	43.7 (39.1–48.4)	0.004**
1987–1996	(10s)	–	–	20s	176/406	43.3 (38.6–48.1)	–
Total		566/1540	36.8 (34.3–39.2)		601/1472	40.8 (38.3–43.3)	0.022*
C Sensitization for mites							
Birth year of participants	2006			2016			p value
	Age in 2006	Positive number	Percentage (95% CI)	Age in 2016	Positive number	Percentage (95% CI)	
1957–1966	40s	106/394	26.9 (22.5–31.3)	50s	62/294	21.1 (16.4–25.8)	0.08
1967–1976	30s	174/435	40.0 (35.4–44.6)	40s	139/342	40.6 (35.5–45.8)	0.85
1977–1986	20s	345/711	48.5 (44.9–52.2)	30s	214/430	49.8 (45.1–54.5)	0.68
1987–1996	(10s)	–	–	20s	195/406	48.0 (43.2–52.9)	–
Total		625/1540	40.6 (38.1–43.0)		610/1472	41.4 (38.9–44.0)	0.63
D Prevalence of allergic rhinitis for mites							
Birth year of participants	2006			2016			p value
	Age in 2006	Positive number	Percentage (95% CI)	Age in 2016	Positive number	Percentage (95% CI)	
1957–1966	40s	47/394	11.9 (8.7–15.2)	50s	28/294	9.5 (6.1–12.9)	0.31
1967–1976	30s	71/435	16.3 (12.8–19.8)	40s	66/342	19.3 (15.1–23.5)	0.28
1977–1986	20s	126/711	17.7 (14.9–20.5)	30s	93/430	21.6 (17.7–25.5)	0.10
1987–1996	(10s)	–	–	20s	89/406	21.9 (17.9–25.9)	–
Total		244/1540	15.8 (14.0–17.7)		276/1472	18.8 (16.8–20.7)	0.035*

[†] Positive number of sensitization and prevalence for each group.[‡] Percentages are shown with 95% confidence intervals in parentheses.[§] The differences in population ratios were tested.* $p < 0.05$, ** $p < 0.01$.

show a significant change in sensitization to mites over a decade. Similarly to sensitization, mite-induced AR prevalence did not show significant changes over a decade for participants born in 1977–1986, 1967–1976, 1957–1966 (Table 4D). Therefore, it might be a universal epidemiological finding that birth year group-based prevalence shows no change over a decade when participants are in their 20s or older. We speculate that the most susceptible age for mite-induced PAR might be around 10 years of age or younger than that. Birth year group-based analysis is good for an overview of individuals; although specific changes among individuals are important to understand the dynamics of development and remission of AR.

Spontaneous remission rate in the cohort population after 10 years for JC pollinosis and for mite-induced PAR

A total of 334 subjects participated in both the 2006 and 2016 surveys (Table 5A). Participants in this group were divided into three allergic statuses. Individuals who showed both sensitization and nasal symptoms were classified as having AR; those who showed sensitization but no nasal symptoms were classified as non-progressors (non-prog), and participants who did not show sensitization and nasal symptoms were classified as no sensitization. Remission was defined as a person changing from AR to non-

Table 5

Changes in the allergic status of the cohort population over 10 years.

A Age range in 2016 (in 2006)		Number	Sex	Number
30–39 (20–29)		92	Men	20
			Women	72
40–49 (30–39)		113	Men	24
			Women	89
50–59 (40–49)		129	Men	23
			Women	106
Total		334	Men	67
			Women	267
B Cedar		2016		
		Allergic rhinitis	Non-progressor	No sensitization
2006 Allergic rhinitis	110	96 (87.3%) [†]	10 (9.1%)	4 (3.6%)
Non-progressor	51	12 (23.5%)	32 (62.7%)	7 (13.7%)
No sensitization	173	9 (5.2%)	12 (6.9%)	152 (87.9%)
	117 [‡]	54	163	
C Mites		2016		
		Allergic rhinitis	Non-progressor	No sensitization
2006 Allergic rhinitis	47	30 (63.8%)	11 (23.4%)	6 (12.8%)
Non-progressor	82	25 (30.5%)	46 (56.1%)	11 (13.4%)
No sensitization	214	4 (1.9%)	4 (1.9%)	206 (96.3%)
	59	61	223	

[†] Number and percentage of each status in 2016 from the original status in 2006.[‡] Total number in 2016 changed from the three allergic status in 2006.

prog or no sensitization status. After 10 years, 110 people who had JC pollinosis in 2006 had changed status. Of them, 9.1% (10/110) became non-prog with no symptoms, and 3.6% (4/110) recovered from AR with no symptoms and negative specific IgE score (Table 5B). Spontaneous remission occurred in 12.7% (14/110) of patients with JC pollinosis. In contrast, there were 21 new-onset cases from non-prog or no sensitization to AR, accounting for 9.4% (21/224) of people with AR in 2016. Of the population in 2006, decrease of remission numbers and increase of new-onset cases resulted in an overall increase in JC pollinosis from 110 to 117 people. The proportions of AR, non-prog, and no sensitization were 87.3% (96/110), 62.7% (32/51), and 87.9% (152/173), respectively. Therefore, non-prog participants were more likely to change, while change was less likely to occur for AR and no sensitization participants.

The 2016 results for the 47 people who had mite-induced PAR in 2006 revealed that 23.4% (11/47) became non-prog and 12.8% (6/47) became no sensitization, resulting in 36.2% (17/47) experiencing spontaneous remission (Table 5C). There were 29 new cases of AR from non-prog or no sensitization, accounting for 9.8% (29/296) of patients with AR in 2016. These changes resulted in an overall increase in mite-induced PAR prevalence. No change in status was observed in 63.8% (30/47) of AR, 56.1% (46/82) of non-prog, and 96.3% (206/214) of no sensitization participants, indicating that unlike JC pollinosis, greater changes occurred for AR status. A small change was observed for the no sensitization group, similar to what was seen for JC pollinosis. This suggests that people aged ≥ 20 years, who are not sensitized, are unlikely to develop JC pollinosis or mite-induced PAR.

Discussion

In the present study, we investigated whether the rates of JC pollinosis and mite-induced PAR increased. We compared the results of a 2016 cross-sectional study to the results of a 2006 survey. The comparison of the two cross-sectional studies based on birth years revealed that participants born between 1977 and 1986, who were in their 20s in 2006 and in their 30s in 2016, but not in the 1967–1976 or 1957–1966 birth year group showed a significant increase in JC pollinosis prevalence over the past decade. This result suggests that the majority of JC pollinosis initiated before 40 years of age and that it is unlikely that JC pollinosis develops after the age of 40. On the other hand, no age group showed changes in sensitization to mite or prevalence of mite-induced AR, suggesting that the majority of mite-induced AR develops before the age of 30. Therefore, we hypothesized that AR onset occurs before the 20s and continues to develop until the 30s. Thus, the present data derived from two cross-sectional studies and a cohort group that participated in both studies aimed to determine differences in sensitization and prevalence between the two cross-sectional studies, including remission rates and new-onset rates.

In the present cohort population, remission of JC pollinosis occurred in 14 participants (12.7%, 14/110) and new-onset in 21 participants (9.4%, 21/224) over a decade, resulting in a slight increase in prevalence. Moreover, remission of mite-induced AR occurred in 17 participants (36.2%, 17/47) and new-onset in 29 participants (9.8%, 29/296), resulting in a slight increase in prevalence.

The remission rate of mite-induced PAR was higher than that of JC pollinosis. There is a possibility that patients with mite-induced PAR underestimate their nasal symptoms because mite-induced nasal symptoms are less clear compared to JC pollinosis, which is accompanied by a definitive pollen dispersal season and less competitive airborne antigens. However, in our present cohort study, the remission rates of JC pollinosis and mite-induced AR were

almost the same as those reported by Bodtger *et al.* who conducted a cohort study based on interviews with AR patients and examined the serum-specific IgE status of people aged 15–65 years in 1990.¹⁸ The survey was repeated in 1998. The study included 257 participants, and remission was observed in 11.8% of pollinosis cases and 38.2% of mite-induced PAR cases over the eight years. Among the people who exhibited remission of AR symptoms, 78% were no longer positive for serum antigen-specific IgE. They concluded that it is more difficult to avoid seasonal antigens in the atmosphere than mite antigens indoors. Yonekura *et al.* also showed a higher remission rate in mite-induced PAR (61.5%) than in JC pollinosis (19.2%) among participants in their 40s over a decade. The differences in the mechanisms of remission of PAR and SAR need to be elucidated.

The results of the present study suggest that longitudinal prevalence based on birth years consists of initiation periods and stable periods. In initiation periods for JC pollinosis, development of JC pollinosis occurs in the early stage of life and lasts longer because pollen exposure is widespread and abundant annually. On the other hand, we speculate that initiation periods for mite-induced AR development occurs in the early stage of life but lasts less than JC pollinosis because exposure to indoor mite allergens diminishes due to an increase in outdoor activities between school-aged children and adults.

Individuals aged 20–49 years in the present cohort study showed significantly higher new-onset cases of JC pollinosis than individuals aged 40–69 years in the study by Yonekura *et al.* ($p < 0.001$, chi-square test).² Furthermore, in the present study, the rate of new-onset of mite-induced PAR was higher than that reported by Yonekura *et al.* ($p < 0.001$, chi-square test). Although we cannot simply compare Yonekura's data and our data, these results indicate that new onset was more likely to occur in the 20–49-year age group than in the 40–69-year age group. Participants in their 50s were not recruited in the 2006 survey because the University of Fukui Hospital was established in 1983, and most workers were younger than 50 in 2006. This fact resulted in a small number of staff members in their 50s and those were excluded from previous study. However, we recruited participants in their 50s in the 2016 survey because participants in their 40s in 2006, who would have reached their 50s in 2016, were critical. When data of participants in their 50s were excluded from the 2016 survey, sensitization of JC pollen and mites was 59.5% (701/1178) and 46.5% (548/1178), respectively. The prevalence of JC pollinosis and mite-induced PAR was 41.1% (484/1178) and 21.1% (248/1178), respectively.

Because this study recruited a population working in hospitals, it may have been biased in terms of occupational uniformity. Additionally, the fact that most hospital workers are women could serve as another source of bias. For these reasons, this study may not accurately reflect the situation of the general population. However, no significant differences in sensitization and prevalence rates were observed among hospital staff professions (data not shown). The cohort population included several people who participated in the first cross-sectional study. People with AR symptoms were more likely to participate in the second survey, and those assessed as not having AR in the first survey were more likely to refuse to take part in the second, which introduced some systematic bias.

Participants who reported no past nasal symptoms for more than two consecutive JC pollen seasons or perennial periods in the questionnaire were considered to have negative nasal symptoms. Those who showed negative nasal symptoms or negative specific IgE scores were defined as remission in the present cohort study. This definition might be controversial, as other studies used longer periods to define remission. Additionally, we interviewed those who showed JC pollinosis remission for follow up on nasal symptoms. We confirmed that all of them showed no nasal symptoms in 2017 and 2018 (data not shown).

Among those who were categorized as remission in this cohort group, all showed stable or decreased IgE titers. No individuals showed an increase in IgE titer. In the remission group, JC pollinosis showed a significant decrease in JC-specific IgE levels, from 18.5 ± 25.8 in 2006 to 11.2 ± 18.9 in 2016 ($p < 0.01$). In the new onset group, JC pollinosis showed an increase in JC-specific IgE levels, from 5.6 ± 11.9 in 2006 to 9.9 ± 13.8 in 2016 ($p < 0.01$). However, mite-induced AR showed no change in total and mite-specific IgE levels in the remission and new onset groups (data not shown). These results indicate that there were no specific characteristic features such as age, sex, number of sensitized antigens, and comorbidity with other allergic diseases in the JC pollinosis and mite-induced AR remission and new onset groups. Despite these limitations, we believe our observations of the changes in prevalence rates among subjects who participated in the 2 cross-sectional studies are useful.

In summary, we conducted an epidemiologic survey in 2016. The rates of JC pollinosis and mite-induced AR based on birth year groups showed that only in the younger birth year group JC pollinosis increased, suggesting that AR initiates before 20 years of age, followed by periods of stability observed over a decade. Additionally, both of JC pollinosis and mite-induced AR showed remission but also new onsets, resulting in a slight increase over a decade.

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Conflict of interest

The authors have no conflict of interest to declare.

Authors' contributions

MS and SF designed the study and co-wrote the manuscript. MS, TTs, SK, YujiK, KY, YKi, YukiK, MK, KO, YI, MO, TTa, and NN contributed to data collection. TTa contributed to the statistical analysis of the data. SF supervised the research. All authors approved the final version of the manuscript, agreed to be held accountable

for all aspects of the work, and ensured that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

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