

Analysis of Natural History of Japanese Cedar Pollinosis

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Key Words

Japanese cedar pollinosis · Japanese cedar pollen ·
Remission, spontaneous · Aging · Serum IgE antibody ·
Cross-sectional study · Vertical-sectional study

Abstract

Background: The marked increase in the incidence of Japanese cedar (*Cryptomeria japonica*; JC) pollinosis is a social problem in Japan. Elucidation of its natural history is, therefore, essential. **Methods:** Cross-sectional and vertical-sectional studies were performed regarding the effects of aging on sensitization to Japanese cedar pollen (JCP) and development of JC pollinosis by measuring serum IgE titers to JCP and by oral examination of residents of the Maruyama Town, Chiba, Japan from 1995 to 2001. We also studied the incidence of its spontaneous remission and the background factors. **Results:** In a vertical-sectional study, the serum IgE titer to JCP was strongly influenced by the amounts of pollen scattered. An increase in age by 6 years did not reduce the IgE titer to JCP in subjects in their 40s. However, in subjects aged 60 or more, annual differences in the JCP count did not affect serum IgE titer to JCP, which remained low even after a season with a high pollen count. In subjects with JC pollinosis aged over 40 showing a CAP RAST score of more than 2 to JCP in 1995, spontaneous remission of JC pollinosis was observed in 16.1% over a period of 6

years. Factors affecting spontaneous remission include sex, age at the time, serum IgE titer to JCP and age at first onset of JC pollinosis. **Conclusions:** The CAP RAST score was strongly associated with spontaneous remission in the multivariable model.

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Introduction

Allergic diseases are increasing worldwide [1–5]. In particular, increases in Japanese cedar (JC) pollinosis are becoming a social problem in Japan. Accordingly, we conducted cross-sectional research on sensitization to Japanese cedar pollen (JCP) and prevalence of JC pollinosis among residents including children and adults in a town located on the Boso Peninsula of the Chiba Prefecture. Subjects were followed up over a period of 6 years from 1995 to 2001 to study the effect of aging on the serum IgE antibody titer to JCP, the development of JC pollinosis in those who had a positive serum IgE antibody titer to JCP, the incidence of spontaneous remission and the background factors. Because only 40 years have passed since the first report on JC pollinosis, there has been almost no report on the effect of aging on sensitization to JCP and the development of JC pollinosis. To take long-term measures against JC pollinosis, it is necessary to understand the natural history of the disease.

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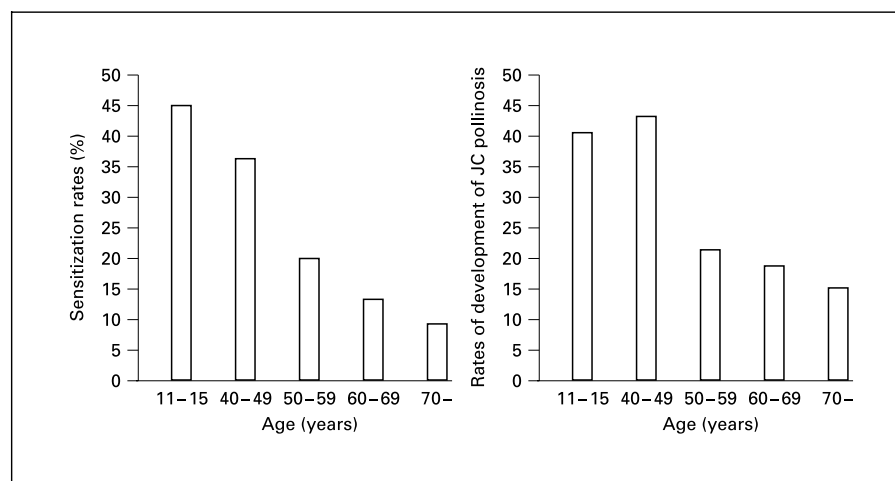
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Fig. 1. Positive rates for serum IgE antibody to JCP (percentage of subjects with CAP RAST score of ≥ 2) and rates of development of JC pollinosis in subjects positive for the antibody (1995).



Subjects and Methods

As part of the medical examination of adult residents of the Maruyama Town, Awa-gun, Chiba Prefecture, located towards the southern tip of the Boso Peninsula, a questionnaire survey was conducted to determine whether they had developed JC pollinosis. This study was performed in June 1995. In this area, the JCP season is from early January to April. In 1995, the pollen count was high in this area. Among the local residents, 1,560 adults (647 men and 913 women) participated in the study; written informed consent was obtained after having adequately explained the objective of the study and its procedures. Serum IgE antibodies to JCP and to mites (*Dermatophagoides pteronyssinus*) were determined to investigate the sensitization rates of JC pollinosis and of mite allergic rhinitis to these antigens in all residents and any difference in the prevalence rate by age (cross-sectional research). Similar investigations were conducted with 292 children aged 11–15 years as part of the medical examination at elementary schools and junior high schools in the same district.

In June 1996, when the JCP count was low, medical examination, questionnaire survey and determinations of serum IgE antibody titer antibodies to JCP were conducted in the same 135 junior high school students who were examined in 1995, a year with a high pollen count.

In the same adult subjects who were examined in 1995, medical examination, questionnaire survey and measurement of serum IgE antibody titers to JCP and to mites were also conducted in 1999, 2000 and 2001 to investigate the changes in the above antibody titers as well as changes in rates of development of JC pollinosis and mite allergic rhinitis with aging (vertical-sectional research). Incidences of multiple sensitization to *Dactylis glomerata* and *Artemisia* were also examined in 2000.

Incidences of spontaneous remission and background factors of JC pollinosis were examined in subjects who had developed JC pollinosis symptoms in at least three successive seasons by 1995 and showed serum CAP (Pharmacia CAP System) radioallergosorbent test (RAST) score above 2 in 1995 and whose serum IgE antibody titers to JCP were measured more than once during the 3 years from 1999 to 2001. The specific antibody level (CAP RAST score) was classified as follows: score 6 = higher than 100 UA/ml; score 5 =

50.0–99.9 UA/ml; score 4 = 17.5–49.9 UA/ml; score 3 = 3.50–17.4 UA/ml; score 2 = 0.70–3.49 UA/ml; score 1 = 0.35–0.69 UA/ml; score 0 = less than 0.34 UA/ml. Generally a CAP RAST score of 2 or more is regarded as positive, a score of 0 is negative, and a score of 1 is equivocal.

A follow-up survey was conducted from 1995 to 2001 in subjects above the age of 40 who had a CAP RAST score to JCP of above 2 but did not develop JC pollinosis in 1995 during the period of the high JCP count to investigate the incidence and background factors of newly developing JC pollinosis after the age of 40 years in addition to the measurement of changes in serum IgE antibody titer to JCP.

Statistical Analysis

A significant difference was assessed by the Fisher exact test for categorical variables and the Mann-Whitney U test for continuous variables. Multiple logistic regression models were employed in order to analyze factors associated with remission and onset. Statistical analysis was performed with the JMP 5.0 (SAS Institute, Cary, N.C., USA).

Results

Changes in Serum IgE Antibody Titers to JCP and to Mites with Aging

Results of Cross-Sectional Research

Figure 1 shows positive rates for serum IgE antibody to JCP (CAP RAST score of ≥ 2) by age as well as rates of development of JC pollinosis by age in 292 elementary school and junior high school students aged 11–15 years measured after the JCP season in 1995. Sensitization rates reached 44.9% at this age. The rate of development of JC pollinosis in children with positive antibody to JCP reached 40.5%. Figure 1 indicates sensitization rates to JCP and rates of development of JC pollinosis compared

Table 1. Comparison of the number of children with JC pollinosis and serum IgE antibody titer to JCP in the same junior high school students between 1995 (high JCP count year) and 1996 (low JCP count year)

IgE antibody titer	Subjects	Mean serum IgE antibody titer to JCP, UA/ml		Number of children with JC pollinosis	
		1995	1996	1995	1996
1995 $\geq$ 1996	121	9.31	5.42	30	43
1995 < 1996	14	2.72	4.35	3	8
Total	135			33	51

with each age group covering 10 years in 1,560 residents over the age of 40. A sharp decrease in sensitization rates with age was observed in subjects over the age of 40. The rate of development of JC pollinosis in subjects positive for IgE antibodies to JCP decreased rapidly over the age of 50 years.

Results of Vertical-Sectional Research

Chronological changes with age in serum IgE antibody titer to JCP were investigated in 162 adult subjects who showed a CAP RAST score ≥ 2 to JCP in 1995 and whose serum IgE antibody titers to JCP were measured in 1999, 2000 and 2001. In the Chiba Prefecture, the JCP count was high in 1995, low in 1999, moderate in 2000 and high in 2001. In subjects in their 40s, serum IgE antibody titers to JCP fluctuated depending on the pollen count and there was no effect of aging on the serum antibody titer to JCP. In subjects in their 60s and 70s, no correlation was observed between fluctuations of serum IgE antibody titers to JCP and the pollen count, while a variation of the antibody titer in subjects in their 50s was intermediate compared to subjects in their 60s and 40s (fig. 2).

Because of the markedly decreased pollen count in 1996 compared to that in 1995, an increase of serum IgE antibody titer to JCP was observed in only 14 children and a decreased titer was seen in 121 of 135 junior high school students who were examined both in 1995, a year with a high pollen count and in 1996, a year with a low pollen count. Despite the above facts, JC pollinosis symptoms were observed in 1996 in all children except 1 of 33 who developed JC pollinosis symptoms in 1995, a year with a high pollen count. Moreover in 1996, 18 children newly developed JC pollinosis of 102 who did not develop the symptoms in 1995 (table 1).

Multiple Sensitization to Other Allergens in Subjects Positive for Serum IgE Antibody to JCP

In the investigation performed in 2000, children corresponding to 76.3, 59.3 and 16.9% of those who showed a

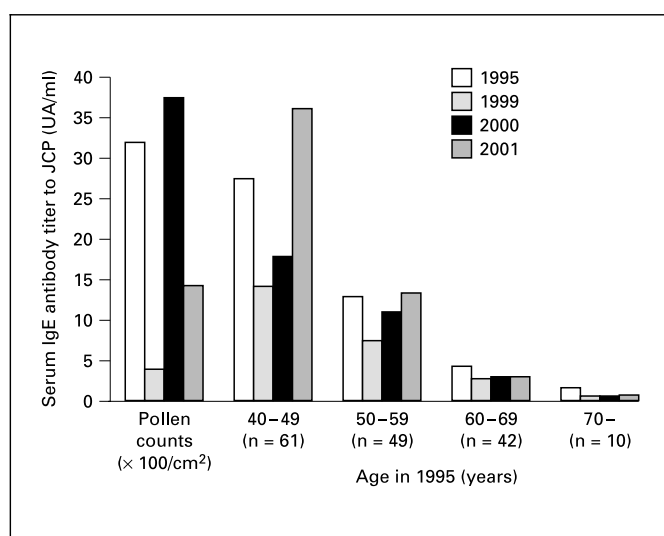


Fig. 2. Fluctuations of serum IgE antibody titer to JCP by age group over the 6 years from 1995 to 2001 in 162 subjects with a CAP RAST score to JC of ≥ 2 in 1995.

CAP RAST score ≥ 2 to JCP were shown to have also been sensitized to mites, *D. glomerata* and *Artemisia*, with a CAP RAST score of ≥ 2 to each allergen. On the other hand, adult subjects aged over 40 years corresponding to 36.8, 54.7 and 23.6% of those who showed a CAP RAST score ≥ 2 to JCP were shown to have also been sensitized to mites, *D. glomerata* and *Artemisia* with a CAP RAST score of ≥ 2 to each allergen. Subjects who had been sensitized with 3 and 4 allergens including JCP were observed in 40.7 and 13.6% of children, respectively, and 25.7 and 10.4% of adults, respectively (fig. 3).

Spontaneous Remission of JC Pollinosis

Among 280 subjects aged over 40 years who showed a CAP RAST score ≥ 2 to JCP in the first examination performed in 1995, 56 subjects developed symptoms of JC pollinosis in more than three successive seasons including

Table 2. Background factors in subjects in whom spontaneous remission of JC pollinosis occurred compared with those who continue to have the disease

	Subjects with spontaneous remission (n = 9)	Subjects without spontaneous remission (n = 47)	p
Age (in 1995), years	61.1	48.7	0.002
Males	7/9	13/47	0.007
Age at the onset, years	50.8	40.2	0.027
Serum IgE antibody titer to JCP in 1995, UA/ml	4.7	40.7	<0.001
Complications by other allergic diseases	5/9	16/47	0.272
Predisposition	0/9	7/47	0.583

There were 280 subjects over the age of 40 in 1995 with a serum CAP RAST score to JCP of ≥ 2 . Of these, 9 were asymptomatic in the last 3 successive pollen seasons (including 2001).

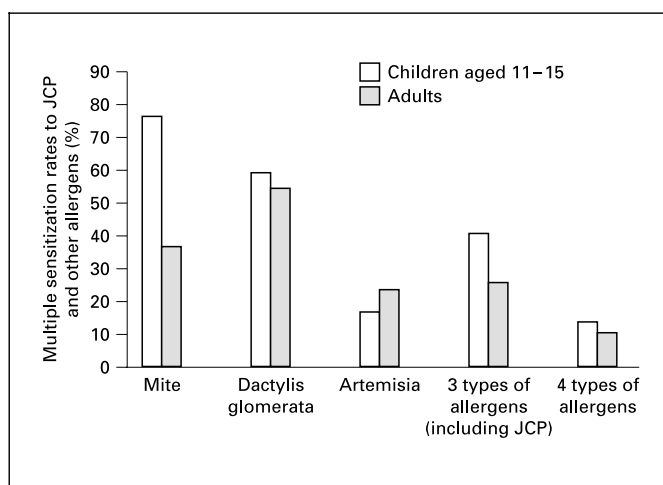


Fig. 3. Multiple sensitization rates (CAP RAST score of ≥ 2) in adult residents (n = 144/1,451) and children (n = 59/158) positive for JC antibody in 2000.

1995, and the serum IgE antibody titers to JCP were measured more than twice by 2001 in these 56 subjects. In 9 subjects among them, no JC pollinosis symptoms were observed during the last three seasons or more including 2001, a year with a high pollen count. These subjects were regarded as cases of spontaneous remission and examined regarding their background factors including age and serum IgE antibody titer to JCP at first examination, age at onset of JC pollinosis, age at disappearance of JC pollinosis symptoms, complications by other allergic diseases including perennial allergic rhinitis and their correlation with the incidence of predisposition (history of JC polli-

nosis in their parents, brothers and sisters). Serum IgE antibody titers to JCP in 1995 were 4.7 UA/ml in the spontaneous remission group and 40.7 UA/ml in the non-remission group. The comparison of their background factors with those of 47 subjects who continued to show JC pollinosis symptoms successively over the same periods of time demonstrated significant differences in sex, age at onset of JC pollinosis, age at first examination, and serum IgE antibody titer to JCP (table 2). In addition, the CAP RAST score was strongly associated with spontaneous remission in the multivariable model [odds ratio (OR) 48.99; 95% confidence interval (CI) 4.17–2,204.96]. In multivariate analysis, there was no significant effect on sex, age (in 1995) and age at the onset (table 3).

Onset of JC Pollinosis in Middle-Aged and Elderly Persons

Showing a CAP RAST score ≥ 2 to JCP in 1995, a year of an abundance of scattered JCP, 182 subjects over the age of 40 did not develop JC pollinosis. Among these subjects, serum IgE antibody to JCP was measured in a total of 151 subjects over the years 1999, 2000 and 2001, and 19 of these subjects developed JC pollinosis in the 6 years since 1995. Comparison of age, sex, complication, predisposition and serum IgE antibody titer to JCP of these subjects with those of subjects who did not develop JC pollinosis in these periods of time revealed that the mean age of the former is 50.7 years and that of the latter is 58.7 years, with the former age being significantly lower (table 4). In a multivariate analysis, age was associated with a lower risk of onset (OR 0.49 per 10 years; 95% CI 0.26–0.86). Predisposition was related to a higher risk (OR 5.06; 95% CI 0.94–22.80) (table 5). Since the number of

Table 3. Factors of spontaneous remission of JC pollinosis

Factor	OR	95% CI	p
Age (in 1995; per 10 years)	1.31	0.36–5.50	0.681
Male	9.49	0.90–286.80	0.097
Age at the onset (<40/≥40)	0.26	0.01–8.89	0.469
CAP RAST score (2/>2)	48.99	4.17–2,204.96	0.009
Complications by other allergic diseases	0.31	0.01–4.17	0.384

Table 4. Background factors in subjects who newly developed JC pollinosis after reaching 40 years of age compared with subjects positive for serum IgE to JCP who had not developed the disease

	Subjects who developed the disease (n = 19)	Subjects who did not develop the disease (n = 163)	p
Age (in 1995)	50.7	58.7	0.003
Males/females	10/19	99/163	0.622
Serum IgE antibody titer to JCP in 1995, UA/ml	24.5	4.8	0.118
Complications by other allergic diseases	0/19	9/163	0.008
Predisposition	3/19	7/163	0.073

There were 280 subjects over the age of 40 in 1995 with a CAP RAST score to JCP of ≥ 2 . A total of 182 subjects had not developed symptoms of the disease by 1995. Of these, 19 subjects developed JC pollinosis in 1996 or thereafter.

Table 5. Factors of onset of JC pollinosis

Factor	OR	95% CI	p
Age (in 1995; per 10 years)	0.49	0.26–0.86	0.019
Male	1.03	0.33–2.95	0.963
CAP RAST score (2/>2)	0.55	0.18–1.73	0.296
Complications by other allergic diseases	4.08	0.91–17.09	0.057
Predisposition	5.06	0.94–22.80	0.040

subjects who newly developed the disease was larger than that of those in whom spontaneous remission occurred in their 40s, the prevalence rate of JC pollinosis in subjects positive for antibody to JCP increased with age. On the other hand, in subjects in their 60s or older, the incidence of subjects developing the disease newly decreased and the number of subjects in whom spontaneous remission occurred increased. Accordingly, a prevalence rate of JC pollinosis in subjects over the age of 60 positive for serum IgE antibody to JCP in 1995 decreased with age or remained low at the same level. The variation of the prev-

alence rate of JC pollinosis in patients in their 50s was intermediate in its pattern compared with that in patients in their 60s and 40s (fig. 4).

Discussion

In childhood, the sensitization rate to JCP and the prevalence rate of JC pollinosis increased with age, and subjects who developed the symptoms of JC pollinosis once continued to have it in the next pollen season even

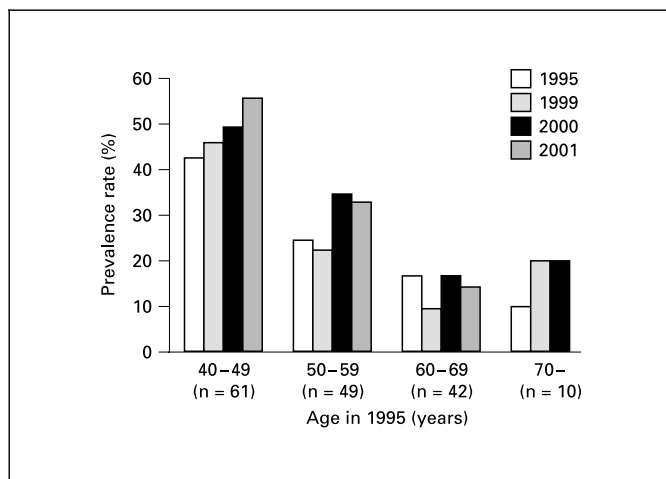


Fig. 4. Fluctuations of prevalence rates of JC pollinosis over a 6-year period in subjects with a serum CAP RAST score to JC of ≥ 2 by age group.

when the amounts of scattered JCP were remarkably reduced. Spontaneous remission hardly occurred at this age. In vertical-sectional research where the same adult subjects were followed up for 6 years, serum IgE antibody titer to mites significantly decreased with age in subjects over the age of 40 who were positive for serum IgE antibody to mites but this was not accompanied by double sensitization to JCP. It is considered that the potential of IgE production in B lymphocytes to mites antigen decreases with age from the age of 40 onward [6-9]. However in subjects with JC pollinosis serum IgE antibody titers to JCP did not decrease over a 6-year period in subjects in their 40s, and the IgE antibody titers to JCP are strongly influenced by the amount of pollens scattered. The difference in the variation of antibody titers to different antigens might have arisen from the difference in the amounts of antigen exposed and in the degree of their antigenic potency between patients with JC pollinosis and those with perennial allergic rhinitis due to mites. After the age of 60 years, differences in the amounts of JCP scattered did not affect the IgE antibody titer to JCP, while at the age of 50, the variation of the titer was intermediate in its pattern compared to those at the age of 60 and 40. The above data are in agreement with the fact that spontaneous remission of JC pollinosis was observed in subjects from the age of their late 40s and at the highest incidence in those in their 60s.

There have been very few reports on spontaneous remission of pollinosis, while there are large differences in

the spontaneous remission rates given by different authors. From the results of a follow-up study in 738 university students with pollinosis conducted 23 years after graduation from the university, Greisner et al. [10] reported that the symptoms of pollinosis disappeared in 22.9% of the subjects, while they remained but were improved in 32%, remained unchanged in 33.3% and were exacerbated in 9.2%. For evaluating the results, however, changes in the environment as regards exposure to pollens due to changing their place of residence after graduation should be taken into consideration. Broder et al. [11] reported that spontaneous remission of pollinosis was observed in 5% of females and 10% of males during a 5-year follow-up period in examinations of 6,563 residents with a high incidence of spontaneous remission in subjects aged 45 years or more. On the other hand, Danielsson and Jessen [12] reported after their 12-year follow-up of 82 subjects that a disappearance of JC pollinosis symptoms was observed only in 1.2% (1/82), while the symptoms were improved, remained unchanged and worsened in 39, 39 and 21% of subjects, respectively. According to Smith [13], 10 (8.9%) of 112 children became asymptomatic 5 years later. Since there are significant differences in the incidence of spontaneous remission of allergic rhinitis for all types of antigen, the amount of antigen to which the subjects are exposed, age distribution, severity of the disease and the length of the follow-up period, and a consolidation of the definition itself of the term of spontaneous remission are considered necessary.

When the subjects studied were limited to those whose ages at first examination were over 40 and whose CAP RAST scores to JCP were more than 2, spontaneous remission was observed in 16.1% of subjects in the 6-year follow-up period. Although spontaneous remission rates of JC pollinosis are significantly higher in subjects over the age of 60, the overall rate in subjects including children was several percent lower than reported until now. Cases in which spontaneous remission cannot be expected will likely increase, as children with JC pollinosis and patients with a predisposition to JC pollinosis increase.

Since there might be large differences in environmental factors from childhood to the age of onset of pollinosis, including diet, residence and many other factors between patients with JC pollinosis aged 10-20 at present and those aged 60 or more, it is difficult to predict and compare future incidences of spontaneous remission in these two groups in a similar straight line. Further long-term vertical-sectional follow-up research is required to understand the natural history of JC pollinosis.

References

- 1 Sibbald B, Strachan DP: Epidemiology of rhinitis; in Busse NW, Holgate ST (eds): *Asthma and Rhinitis*. Boston, Blackwell Science, 1995, pp 32–43.
- 2 Wüthrich B: Epidemiology of the allergic diseases: Are they really on the increase? *Int Arch Allergy Appl Immunol* 1989;90:3–10.
- 3 Nakamura S: Investigation into the frequency of cases Japanese cedar pollinosis among university students in the year of freshmen and fourth-grade (in Japanese). *Jpn J Allergol* 1993; 42:101–106.
- 4 Ishizaki T, Koizumi K, Ikemori R, Ishiyama Y, Kushibiki E: Studies of prevalence of Japanese cedar pollinosis among residents in a densely cultivated area. *Ann Allergy* 1987;58:265–270.
- 5 Wüthrich B, Schindler C, Leuenberger P, Ackermann-Lieblich U: Prevalence of atopy and pollinosis in the adult population of Switzerland (SAPALDIA study). *Swiss Study on Air Pollution and Lung Diseases in Adults*. *Int Arch Allergy Immunol* 1995;106:149–156.
- 6 Edelstein DR: Aging of the normal nose in adults. *Laryngoscope* 1996;106(suppl 81):1–25.
- 7 Droste JHJ, Kerkhof M, de Monchy JGR, Schouten JP, Rijcken B: Association of skin test reactivity, specific IgE, total IgE, and eosinophils with nasal symptoms in a community-based population study. The Dutch ECRHS Group. *J Allergy Clin Immunol* 1996;97:922–932.
- 8 Hanneuse Y, Delespesse G, Hudson D, Halleux F: Influence of aging on IgE mediated reactions in allergic patients. *Clin Allergy* 1978; 8:165–174.
- 9 Delespesse G, Maubeuge J, Kennes B, Nicaise R, Govaerts A: IgE mediated hypersensitivity in aging. *Clin Allergy* 1977;7:155–160.
- 10 Greisner WA, Settipane RJ, Settipane GA: Natural history of hay fever: A 23-year follow-up of college students. *Allergy Asthma Proc* 1998;19:271–275.
- 11 Broder I, Higgins MW, Mathews KP, Keller JB: Epidemiology of asthma and allergic rhinitis in the whole community. *J Allergy Clin Immunol* 1974;54:100–110.
- 12 Danielsson J, Jessen M: The natural course of allergic rhinitis during 12 years of follow-up. *Allergy* 1997;52:331–334.
- 13 Smith JM: A five-year prospective survey of rural children with asthma and hay fever. *J Allergy* 1971;47:23–30.