

Exposure to Japanese Cedar Pollen in Early Life and Subsequent Sensitization to Japanese Cedar Pollen

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The effect of exposure to Japanese cedar pollen (JCP) in early life on subsequent sensitization to it was evaluated. Specific IgE antibody to JCP was examined in 440-504 school children in a rural town each year during 1995-98. The amount of dispersed pollen measured by a Durham sampler widely ranged from 165 to 5941 grains/cm²/year during this period. The amount had been measured during the period of 1982-91 in which these children were born, and it also widely ranged from 148 to 8566 grains/cm²/year.

Children born during November to January, who were exposed to JCP within 6 months of age, increased at the risk of sensitization to JCP, especially severe sensitization, relative to those born in the other months. Age-adjusted prevalence rate ratio (RR) of having a JCP-IgE ≥ 15 U/ml (control; <0.35 U/ml) for children born in December to February relative to children born in the other months was 1.74 (95% confidence interval; 1.06-2.87, examined in 1998), and for those born in November to January was 1.57 (95% CI; 1.00-2.46, examined in 1997). The risk of sensitization to JCP was low for those born in May to July (RR=0.42, 95%CI; 0.19-0.93, examined in 1998). There was also a strong correlation between the amount of the dispersed pollen during the period of 2-6 months after birth and the prevalence of sensitization to JCP. *J Epidemiol*, 2000 ; 10 : 42-47

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Exposure to an allergen within one year after birth, especially in the neonatal period, is thought to be an important risk factor for sensitization to the allergen. A significant relationship between the risk of sensitization to seasonal allergens such as pollen and month of birth was reported in Western countries ¹⁻¹⁰, but it has not been investigated with regard to Japanese cedar pollen (JCP) in Japan. JCP is a typical seasonal allergen dispersed from late February to early April in Japan, and causes Japanese cedar pollinosis which is the most common hay fever in spring. Pollen from Japanese cypress has cross-antigenicity with JCP and causes symptoms of pollinosis ¹¹. It disperses from late March to late April, and the amounts of dispersion are well correlated with JCP ¹¹.

In this study, we focused on the effect of exposure to JCP in the early neonatal period on subsequent sensitization to JCP in a general population. Difference in prevalence of sensitization to JCP by month of birth and by birth year was examined since JCP is a seasonal allergen and the dispersion of JCP varies year by year because of climate.

Sensitization to a specific allergen is evaluated by the level of the specific IgE antibody. The level depends on the amount of dispersed pollen in the examination year, i.e., the strength of exposure to the allergen, and the dispersion is widely different by year. Therefore, the study is desirable to be conducted in different years.

Most of the previous studies targeted patients with allergy

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except for Wjst's report ⁴⁹⁾. A study in a general population is more valuable than case studies because the prevalence of sensitization is evaluated and potential biases are avoided. In addition, the same analysis was done in this study for house dust mite (HDM) for reference.

METHODS

The subjects were all children attending primary or junior high schools in a rural town, who were 6-14 years old in April each year during 1995-1998 and they were 595, 586, 559 and 534 children, respectively, in those years. Therefore, many of them were examined repeatedly during their school age, and 6-year-old children were recruited in and 15-year-old children went out of the subjects every year. The serum examination of specific IgE antibody to JCP and HDM (JCP- and HDM-IgE) was conducted every year from 1995 to 98. Parental informed consent was required in writing in advance of the examination. The examinees were 498, 504, 458 and 440 children in 1995-98, respectively. The subjects comprised 82-86% of all children in those schools each year. The distribution of birth years is shown in Table 1. The population of the town is around 6000 and it is located in a hilly region of southern Kyoto Prefecture. There is one primary school and a junior high school in the town, and hardly any children go to other schools outside the town, so most of the graduates from the primary school go to the junior high school.

A Vaseline-coated slide glass is set outside for 24 hours using a Durham sampler and the number of naturally fallen pollen grains collected on the slide is counted. The measurement is presented as the number of pollen grains per square centimeter on the glass ^{11, 12)}. The measurement for a specific year is presented as the summation of all counts during the season. Correlation coefficients between the amounts of pollen measured by the Durham's method and that by the Burkard sampler were reported around 0.6 to 0.8 ^{11, 13)}.

Every year since 1982, the amount of dispersed JCP has been recorded in Kyoto city by the Department of Otorhinolaryngology of Kyoto Prefectural University

of Medicine (Table 1). The town is around 25km from the University and the actual amount of dispersed pollen in the town has been measured since 1994. The JCP counts were 165, 5941, 663, 2007 and 799 grains/cm² in the study area in 1994-98, respectively, and 227, 9440, 321, 1310 and 285 at the University during the same period. Both measurements were well correlated (Spearman's correlation coefficient=0.90, $p=0.04$), therefore the measurement at the University can be used as a valid indicator of the severity of JCP exposure in the town during 1982-91.

In May every year, JCP- and HDM-IgE were measured using the Pharmacia CAP System at SRL, Inc., Japan. Standardization of measurements over the years was conducted using a control serum of SRL, and drifts in the measurements were kept within tolerable limits. Measurements were presented by CAP score. The lower limit of CAP score 1 was 0.35 U/ml, i.e., the lowest detection limit. CAP score 4 is equivalent to 15 U/ml or higher.

The age-adjusted prevalent rate ratio of sensitization was calculated by the PHREG procedure using SAS ^{14, 15)}. Prevalent rate ratio was recommended by Lee ¹⁵⁾ to evaluate a relative risk in a cross-sectional study because it resembles to the true value of relative risk than an odds ratio, especially in case of high prevalence of target condition. We thought that the structure of our data were adequate to his model. The risk of sensitization to JCP or HDM was calculated as a rate ratio of having a JCP- or HDM-IgE CAP score ≥ 1 relative to having a CAP score=0. The risk of severe sensitization was also calculated as a rate ratio of having a CAP score ≥ 4 relative to having a CAP score=0. An age-adjusted rate ratio was calculated since the prevalence of sensitization to JCP or HDM was thought to be high among old children.

The risk of month of birth was calculated by the three-month moving method, e.g., the risk for November was calculated as the risk of children born in October to December relative to those born in the other months than those three months. The association between the amount of dispersed pollen in early life and the prevalence of sensitization was evaluated by Spearman's correlation coefficient.

Table 1. The counts of dispersed Japanese cedar pollen since 1982 and the number of the subjects classified by birth year.

Birth year	1980	81	82	83	84	85	86	87	88	89	90	91	92	Total
Count of pollen	NA	NA	2365	398	8566	3043	1632	481	1389	148	995	2220	297	—
No. of subjects, 1995	45	46	56	67	61	50	65	57	40	11				498
1996		34	49	62	68	53	64	58	44	63	9			504
1997			38	56	58	50	61	49	38	62	34	12		458
1998				42	57	51	59	46	35	59	31	47	13	440

* Japanese cedar pollen was measured at the University. The number is the sum of daily counts (grains/cm²).
N.A.; not available.

RESULTS

Prevalence of being positive to JCP and HDM (CAP score ≥ 1) by age is shown in Table 2, which shows a high prevalence among old children. Figures 1 and 2 show prevalence rate ratios (RRs) of sensitization to JCP and HDM for month of birth. The risk of sensitization to JCP increased among children born in winter and decreased among those born in summer. The risk of severe sensitization showed this tendency markedly. Examinations in different years (1995-98) showed the similar results. For examples, birth in January (examined in 1998, RR=1.74, 95% confidence interval; 1.06-2.87) and in December (examined in 1997, RR=1.57, 95%CI;

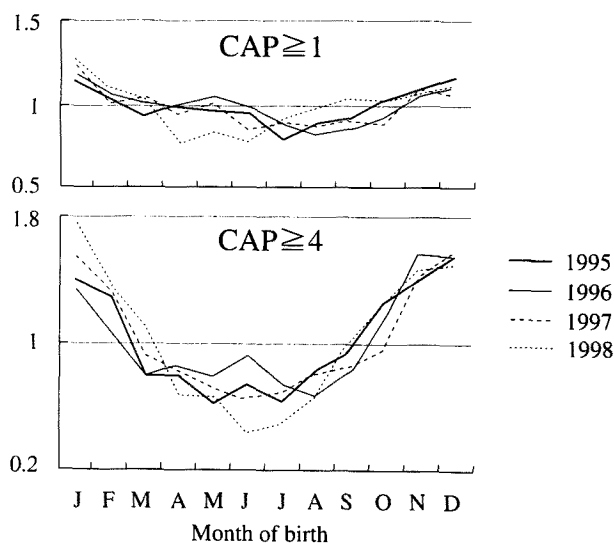
1.00-2.46) had a significantly high risk of severe sensitization and birth in June (examined in 1998, RR=0.42, 95%CI; 0.19-0.93) had the significantly low risk. As for HDM (Figure 2), the risk was high in early summer and in winter, but all of the calculated risks were with p-values more than 0.05.

The risk of sensitization to JCP was almost the same between years of examination although exposure to JCP (the amount of dispersed pollen) was absolutely different year by year and the prevalence of being positive to JCP was also different (high in a large dispersion year). Whereas, the prevalence of being positive to HDM was almost the same between years of examination.

Figures 3 and 4 targeted the examinees in 1997 because

Table 2. Prevalence of being positive to JCP or HDM (CAP score ≥ 1) by age.

		Year of examination			
	Age	1995	1996	1997	1998
JCP	6-8	47.1%	33.9%	33.8%	34.1%
	9-11	57.2%	45.3%	50.9%	43.7%
	12-14	63.4%	52.7%	50.9%	50.9%
HDM	6-8	33.5%	32.1%	32.3%	31.1%
	9-11	43.9%	40.0%	42.8%	40.7%
	12-14	51.8%	47.8%	43.0%	47.3%



The risks in Figures 1 and 2 were calculated for the exact month of birth and neighboring months relative to the other months than those three months (three-month moving method).

Figure 1. Prevalence rate ratio of sensitization to JCP for month of birth.

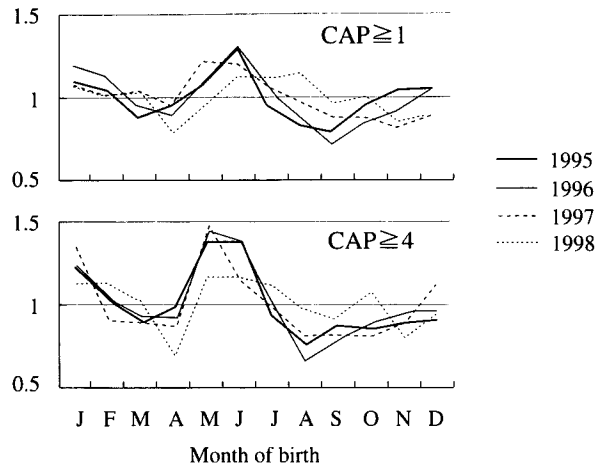


Figure 2. Prevalence rate ratio of sensitization to HDM for month of birth.

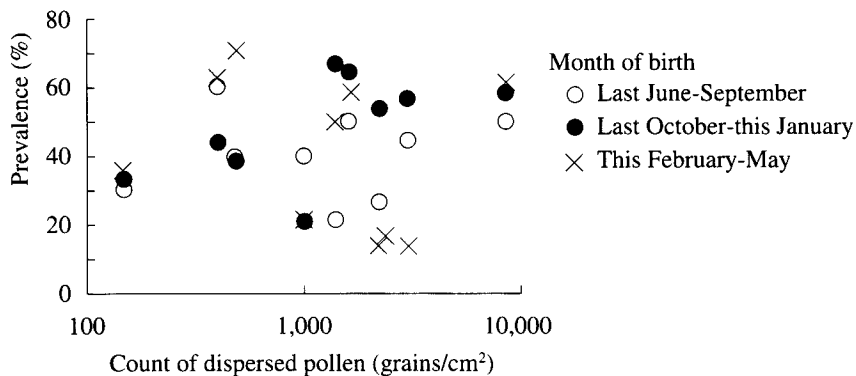


Figure 3. Correlation between the amount of dispersed JCP around the subjects' birth and prevalence (%) of positivity to JCP (CAP score ≥ 1), 1997.

results in the other years were similar to the results in 1997 and the amount of dispersed pollen was moderate in that year. In these figures, the X-axis shows the amount of dispersed JCP in 1982-91, and the Y-axis shows the prevalence of being positive to JCP-IgE (CAP score ≥ 1 in Figure 3 and ≥ 4 in Figure 4). Symbol X shows the prevalence of being positive to JCP among children born during February to May, the spring when JCP was dispersing at the level shown on the X-axis. Closed circles (●) show the prevalence among children born during October to January previous to the spring, who were exposed to JCP at the level shown on the X-axis at ages of 2 to 6 months. Open circles (○) show the prevalence among children born during June to September of the previous year, who were exposed to JCP at ages of 6 to 10 months.

Figure 3 shows that children born during October to January prior to a large-dispersion year were more likely to be positive to JCP (CAP score ≥ 1 for JCP-IgE), and the Spearman's corre-

lation coefficient was 0.61 ($p=0.08$). The prevalence was around 60% when the count of JCP was 1000 grains/cm² or more, while the rate was around 40% or less when the count was less than 1000. Prevalence of sensitization for children born during October to January prior to a small-dispersion year and for those born in the other months prior to either small- or large-dispersion year was almost similar. Children born during June to September and those born during February to May did not show a positive correlation ($r=0.12$, $p>0.5$ and $r=-0.40$, $p=0.32$, respectively).

Figure 4 shows a stronger correlation ($r=0.73$, $p=0.02$) between the amount of JCP and the prevalence of a CAP score ≥ 4 among children born during October to January than the correlation for a CAP score ≥ 1 among them in Figure 3. The prevalence was around 20-40% when the JCP count was 1000 grains/cm² or more, whereas the rate was around 10% or less when the count was less than that. Children born during

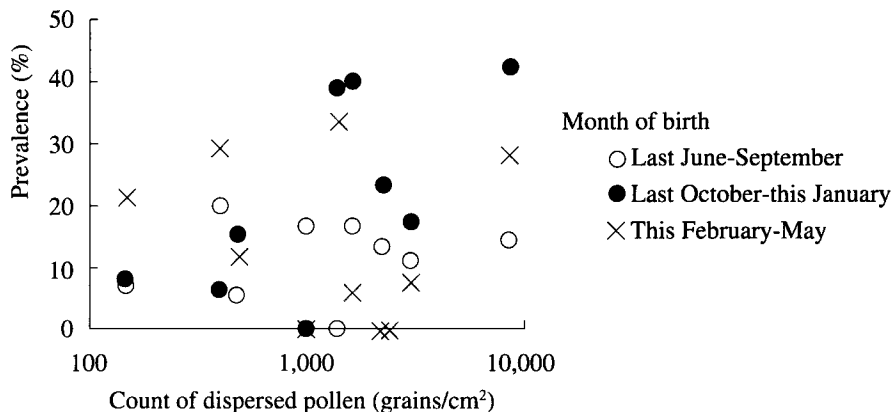


Figure 4. Correlation between the amount of dispersed JCP around the subjects' birth and prevalence (%) of positivity to JCP (CAP score ≥ 4), 1997.

other months showed the similar results as that of being CAP score ≥ 1 .

Age-adjusted prevalence rate ratios of sensitization to JCP for children born during October to January prior to a year in which the count of JCP was 1000 grains/cm² or more relative to children born in the same months prior to a year in which the count was less than 1,000 grains/cm² were 1.66 to 1.85 in the examinations during 1995-98. Those ratios of severe sensitization were 2.21 to 3.66. Most of those risks were significant ($p < 0.05$).

DISCUSSION

Effect of month of birth and varied amount of dispersed JCP by year (ranging from 148 to 8566 grains/cm² during 1982-91) on sensitization to JCP among children was evaluated in this study. Children born during October to February who were first exposed to JCP at an age of 6 months or younger were at increased risk of severe sensitization to JCP (CAP score ≥ 4). This tendency was not remarkable for overall sensitization (CAP score ≥ 1). The risk of sensitization to HDM was high among children born in early summer because they were exposed, during their early life, to a large amount of HDM growing in summer with high temperature and humidity. The risk was also high among those born in winter probably because most houses are warm in winter and tend to be less well-ventilated recently. However, the seasonal variation on the risk of sensitization to HDM is not significant because of reduced seasonal change in indoor-climate. Monthly trends in both JCP-IgE and HDM-IgE were different, so an aggregation of atopic disposition among children born in specific months was hardly suggested.

The correlation analysis also suggested the tendency that exposure to JCP in early life facilitates sensitization to JCP. Children born during October to January prior to a large-dis-

persion year had a higher risk of sensitization to JCP than those born in the same months prior to a small-dispersion year. Some prevalence rates of sensitization to JCP among children born in June to September or those born in February to May were higher than those rates among children born in October to January prior to a small-dispersion year. It may be because the probability of sensitization is similar among children born during October to January prior to a small-dispersion year and those born in the other months prior to either a small- or large-dispersion year. It may be partially because of random variation due to a relatively small number of subjects from whom those rates were calculated (around twenty).

The notion of enhanced sensitization by exposure to an inhaled antigen in early life is thought that primary sensitization to environmental allergens occurs in infancy or early childhood although the onset of allergy or overt disease occurs in later childhood or adulthood¹⁶. All children manifest serum IgG response to environmental allergens during infancy, and low-grade, but significant, IgE to those allergens is detected in the majority of them. Those low-grade IgE responses are transient in children at low genetic risk for atopy and wane by year 4 or 5 for inhalant allergens, whereas atopic children develop allergy later¹⁶.

Keeping windows and doors closed was reported to considerably reduce the amount of pollen entering a house^{11, 17}. Therefore, sensitization to JCP could be reduced by keeping babies indoors during the JCP-dispersing season, at least during days with dense dispersion.

CONCLUSION

Severe exposure to JCP during the first 2-6 months of life increased the risk of sensitization to JCP in school age children. A difference in the prevalence of sensitization by month of birth, as well as an association between the amounts of JCP

dispersed during the period and the prevalence of sensitization were observed. The risk could be reduced if the exposure is avoided.

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