

Smoking and Risk of Cedar Pollinosis in Japanese Men and Women

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Key Words

Allergic rhinitis • Cedar pollinosis • Cohort study • Risk factors • Smoking

Abstract

Background: Pollinosis induced by the cedar pollen antigen is the most common seasonal allergic reaction in Japan. We aimed to examine the relationship between smoking and risk of cedar pollinosis in a population-based cohort of the Japanese. **Methods:** Study subjects were 12,221 men and women from the Takayama Study cohort who were 35–69 years old at enrollment in 1992. A follow-up survey in 2002 was used to obtain information about four symptoms related to cedar pollinosis. **Results:** A total of 1,000 subjects had cedar pollinosis during the 10-year follow-up. As compared with those who had never smoked, current smokers at the baseline were at a significantly decreased risk of cedar pollinosis after controlling for covariates in men (hazard ratio [HR]: 0.64, 95% CI: 0.50–0.83) as well as in women (HR: 0.64, 95% CI: 0.47–0.88). There was a significant dose-response relationship between the risk of cedar pollinosis and the number of cigarettes smoked each day as well as with the number of years an individual had smoked. A significant risk reduction was observed among men and women who had continued to smoke cigarettes during the follow-up period in comparison with those who had never smoked. There was no risk increase for former smokers at the baseline as well as for those who quit smoking during the follow-up. **Conclu-**

sions: Some components of tobacco may protect against cedar pollinosis. Our finding could provide clues about therapeutic strategies for protection against cedar pollinosis.

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Allergic rhinitis is a common clinical condition in many parts of the world [1, 2]. In Japan, pollinosis induced by a cedar pollen antigen is the most common seasonal allergic reaction. It elicits symptoms including rhinitis and/or conjunctival congestion accompanied by pollen-specific IgE production. A recent review reported that the prevalence of pollinosis was 24.5% in the general population in urban areas and had increased >2.6-fold during the past 20 years [3].

Smoking has been associated with upper and lower airway diseases, such as lung and nasal-sinus cancer and chronic obstructive pulmonary disease. However, the associations between smoking and allergic disorders have yielded conflicting results [4]. Studies on smoking and cedar pollinosis are scarce. To our knowledge, only one study has assessed active smoking and cedar pollinosis in adults [5]. In a cross-sectional study of 1,002 Japanese pregnant women, smoking status was unrelated to allergic rhinitis including cedar pollinosis; OR = 0.98 (95% CI: 0.57–1.62) for current smokers and OR = 1.24 (95% CI: 0.71–2.10) for former smokers as compared with never smokers.

Allergic rhinitis including pollinosis might affect tobacco habits by making it uncomfortable for affected in-

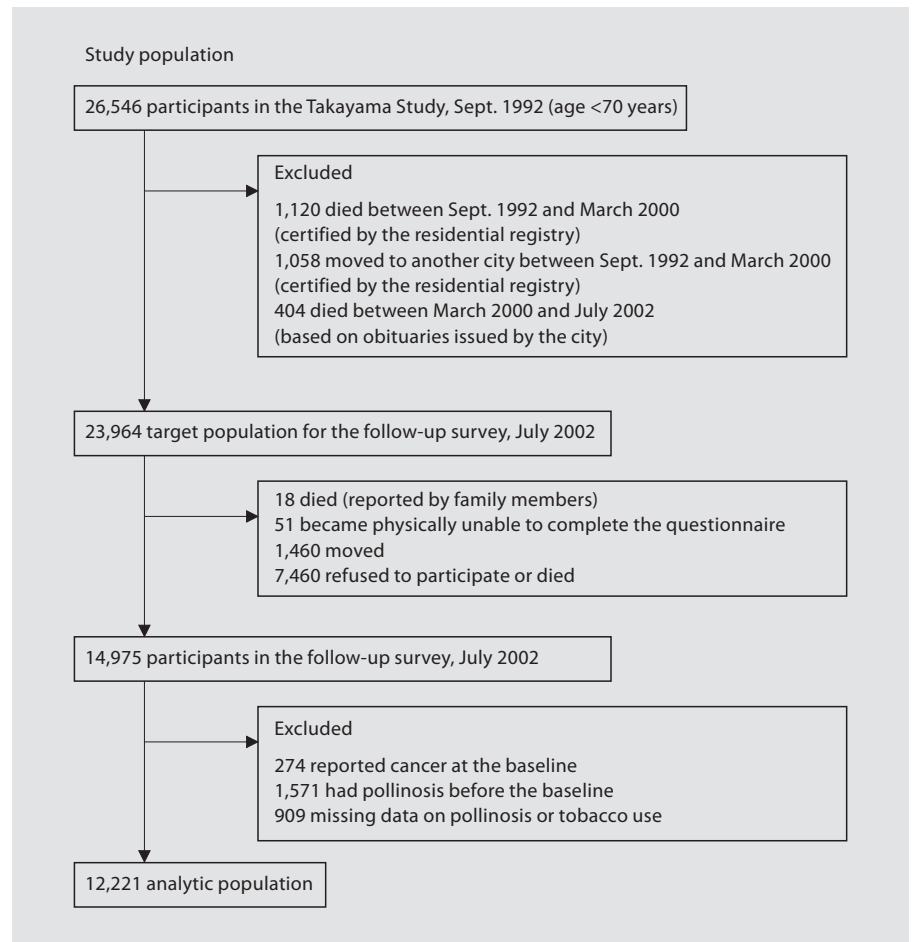


Fig. 1. Flowchart showing the number of study population.

dividuals to smoke. Therefore, the association between smoking and cedar pollinosis should be explored in studies with a longitudinal design. The present study examined the association between smoking status and the development of cedar pollinosis in a cohort of Japanese men and women (Takayama Study). We also assessed the association between the risk of cedar pollinosis and change in tobacco habits between the baseline and the follow-up.

Materials and Methods

Subjects for this study were cohort members from the Takayama Study. The Takayama Study is a population-based cohort study conducted in Takayama City, Gifu, Japan. The methodology of the study design has been described previously [6]. Eligible participants were all the unhospitalized residents of Takayama, aged ≥ 35 years. In 1992, 31,152 persons completed a baseline self-administered questionnaire which included questions on demo-

graphic characteristics, smoking and drinking habits, diet, exercise, and medical and reproductive histories, yielding a participation rate of 85.3%. Smokers were defined as those who had smoked >20 packs of cigarettes before. For current and former smokers, information concerning the number of cigarettes per day they smoked and the number of years they had smoked were asked using categorical response options (≤ 5 , 6–10, 11–20, 21–30, and >30 cigarettes per day and ≤ 10 , 11–20, 21–30, 31–40, and >40 years of smoking, respectively).

The study subjects for the present study were restricted to those who were <70 years of age at the baseline (fig. 1). Residential registry data regarding death and move were only obtained between September 1992 and March 2000. The follow-up questionnaire seeking information about experiences with cedar pollinosis was distributed to 23,964 persons. The response rate after excluding those who were known to be dead or have moved was 66.7%. The baseline characteristics of respondents and non-respondents to the follow-up survey are presented in table 1.

The follow-up questionnaire was developed referring to that reported by Endo [7]. Information was sought about four symptoms of cedar pollinosis, i.e., sneezing, nasal emission, nasal obstruction, and itchy eyes: 'Do you have any of the following symptoms: sneezing, nasal emission, nasal obstruction, or itchy eyes?'

Table 1. Comparison of baseline characteristics between respondents and non-respondents to the second survey

Basic characteristics	Men			Women		
	respondents (n = 6,674)	non-respon- dents (n = 3,528)	p value	respondents (n = 8,301)	non-respon- dents (n = 3,931)	p value
Age, years	52.6	49.0	<0.0001	52.0	50.4	<0.0001
Body mass index, kg/m ²	22.7	22.8	0.13	22.2	22.1	0.57
Alcohol intake, ml/day	43.4	45.2	0.04	7.7	8.9	0.0005
Married, %	94.8	89.7	<0.0001	85.9	81.2	<0.0001
Years of education, %						
≤11 years	52.7	56.8		60.2	64.7	
12–14 years	35.6	32.1		34.8	30.3	
≥15 years	11.7	11.1	0.0003	5.0	5.0	<0.0001
History of allergic diseases, %	6.2	5.9	0.46	9.8	8.6	0.03
Smoking status, %						
Never	16.5	14.6		85.3	77.9	
Former	31.5	22.5		4.9	4.3	
Current	52.0	62.9	<0.0001	9.8	17.8	<0.0001
Occupation, %						
Farming ¹	10.6	10.7	0.87	9.4	10.3	0.13
Furniture making or woodworking ¹	12.3	12.0	0.61	5.4	5.6	0.60
Clerical or office worker ²	10.5	5.5	<0.0001	11.9	7.9	<0.0001

¹ Worked for 10 years or longer.

² Worked the longest.

For each symptom, the following questions were asked: 'If yes, when is the symptom observed? At all times, in the spring only, or at other times?' and 'At what age did the symptom start?' Cedar pollinosis was considered to occur when at least three of the four symptoms were present and at least one of them occurred only during spring. These questions regarding the symptoms and their seasonality do not necessarily define the conditions of cedar pollinosis. Rather, the questionnaire refers to seasonal allergic rhinitis. However, cedar pollen is the most common allergen of seasonal allergic rhinitis as well as allergic rhinitis in Japan. Sakurai et al. [8] estimated that 81.0% of self-reported allergic rhinitis is seasonal rhinitis with symptoms evoked from February to May (the months of pollination of cedar). Of all allergic rhinitis sufferers, 73.5% had symptoms during these months and were cedar-specific IgE-positive (antibody ≥ 0.35 U_A/ml). The ability of the questionnaire to define cedar pollinosis was examined prior to its administration based on diagnoses made by an otolaryngologist using nasal examination, nasal provocation testing, intracutaneous testing, and pollen-specific IgE positivity. The validity study was conducted among 737 subjects (262 men and 475 women) who were recruited from participants in health-check up programs. The sensitivity and specificity were 0.80 (95% CI: 0.77–0.83) and 0.65 (95% CI: 0.61–0.69), respectively [Y. Honda, pers. commun.]. The participants of the present study were asked to record their age when each symptom had first occurred. For identified cases of cedar pollinosis, the individual's age at the onset was determined to be the time when the earliest symptom was observed.

Information on change of smoking status, weight, history of asthma and allergic dermatitis, and other medical conditions was also collected by this questionnaire.

Informed consent was obtained from each subject. This study was approved by the local institutional review board.

The associations of cedar pollinosis with smoking status at the baseline were examined using a Cox proportional hazard model. The specified endpoint of this study was the onset of cedar pollinosis. For each subject, person-years of follow-up were calculated from the study entry (September 1992) to the date of onset of cedar pollinosis or the end of the study (July 2002), whichever came first. The association of cedar pollinosis with change in tobacco use during the follow-up period was examined using a logistic regression model. Analyses were performed separately in men and women and adjusted for the following covariates: age, marital status, years of education, occupational history of farming, body mass index, and alcohol intake.

Misclassification might have occurred when subjects who had had cedar pollinosis before the baseline were identified because the information was obtained 10 years later in the follow-up questionnaire. The questionnaire used at the baseline asked whether individuals had experienced allergies in the past. Examples of diseases in this category included asthma and allergic dermatitis. Although cedar pollinosis was not included as an example, some subjects with cedar pollinosis at the baseline who responded affirmatively to this question may have been misclassified into those without cedar pollinosis at the time of the follow-up survey. Therefore, we reanalyzed data after excluding those who had reported allergies at

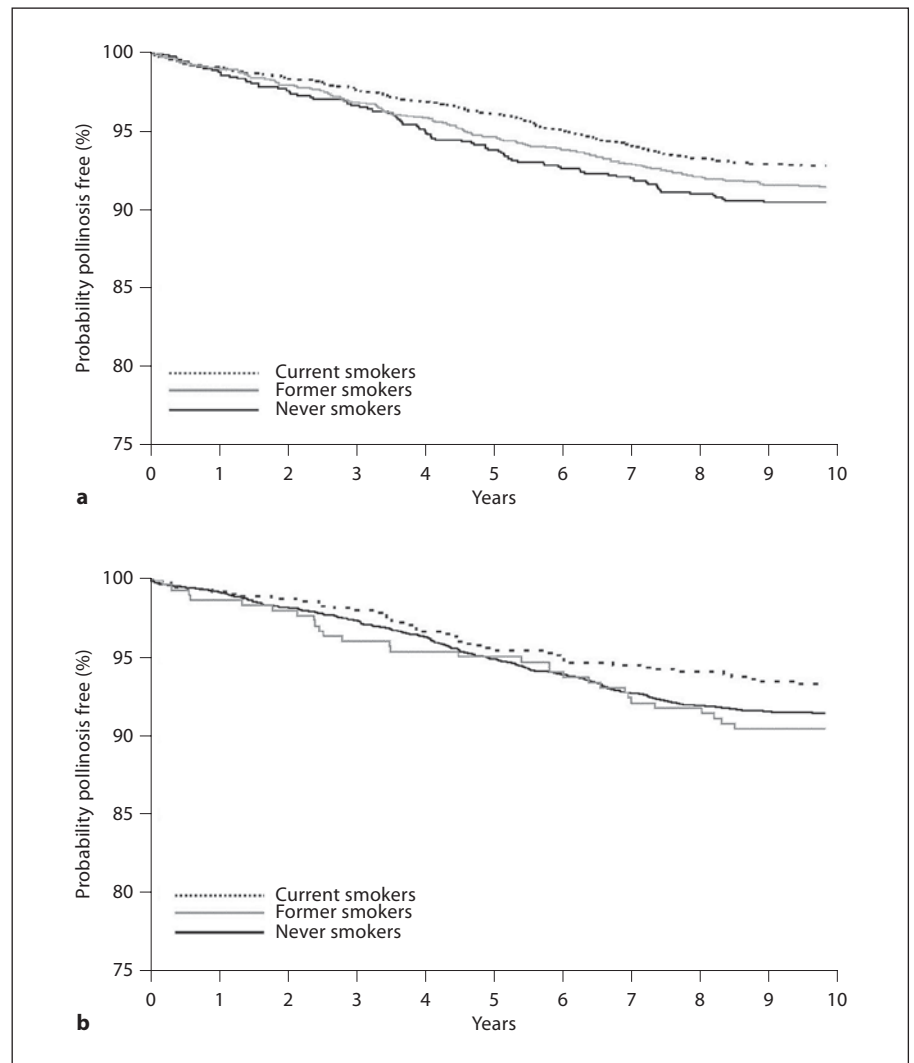


Fig. 2. Kaplan-Meier plots of probability of cedar pollinosis free according to smoking status at baseline in men (a) and women (b).

the baseline. We also repeated analysis excluding those who had the onset of the disease within the first 3 years of the follow-up. We also repeated the analyses after changing the definition of cedar pollinosis to one with a high specificity. In the validity study, the sensitivity and specificity were 0.32 (95% CI: 0.30–0.34) and 0.98 (95% CI: 0.97–0.99), respectively, when cedar pollinosis was defined as a condition in which all four symptoms appeared in the spring. All the statistical analyses were performed using SAS programs.

Results

Baseline characteristics of the study population according to smoking status at the baseline are given in table 2. Smoking status was significantly associated with age, marital status, years of education, occupational history of farming, body mass index, and alcohol intake.

A total of 1,000 cohort members (452 men and 548 women) had cedar pollinosis during the 10-year follow-up. The Kaplan-Meier survival curve showed that current smokers had better disease-free pollinosis survival rates (fig. 2). Table 3 shows the hazard ratios of cedar pollinosis according to smoking status at the baseline. In both men and women, current smokers were at a significantly decreased risk of cedar pollinosis in comparison with those who had never smoked after adjusting for covariates. Former smokers were not at an elevated risk of cedar pollinosis. There was a significant dose-response relationship between the risk of cedar pollinosis and the number of cigarettes smoked each day as well as with the number of years an individual had smoked. Additional adjustments for histories of major chronic diseases such as hypertension and diabetes mellitus, occupational ex-

Table 2. Baseline characteristics of study subjects according to smoking status

Basic characteristics	Men				Women			
	never (n = 924)	former (n = 1,693)	current (n = 3,080)	p value	never (n = 5,553)	former (n = 305)	current (n = 666)	p value
Age, years	52.6	54.7	51.2	<0.0001	52.6	49.9	48.4	<0.0001
Body mass index, kg/m ²	23.0	22.9	22.4	<0.0001	22.2	21.7	21.8	0.0002
Alcohol intake, ml/day	35.3	42.0	46.6	<0.0001	6.4	13.0	15.7	<0.0001
Married, %	94.8	96.4	94.3	0.008	87.6	81.9	76.9	<0.001
Years of education, %								
≤11 years	54.9	57.2	50.3		62.6	52.3	57.8	
12–14 years	35.5	31.7	37.5		32.8	39.4	36.9	
≥15 years	10.6	11.2	12.2	0.0002	4.6	8.3	5.3	0.001
Occupation, %								
Farming ¹	16.2	11.1	9.4	<0.0001	11.2	3.8	2.9	<0.0001
Furniture making or woodworking ¹	13.5	12.8	11.9	0.33	5.6	4.1	4.8	0.40
Clerical or office worker ²	9.2	11.6	10.1	0.11	11.7	11.4	11.7	0.44

¹ Worked for 10 years or longer.² Worked the longest.**Table 3.** Risk of cedar pollinosis according to smoking status at the baseline

	Cases	Person-years	Hazard ratio (95% CI)	
			age-adjusted	multivariate ¹
<i>Men</i>				
Never smokers	88	8,572.7	1.00	
Former smokers	144	15,829.6	0.98 (0.76–1.29)	0.96 (0.73–1.26)
Current smokers	220	29,082.9	0.67 (0.53–0.86)	0.64 (0.50–0.83)
≤10 cigarettes/day	29	3,885.2	0.76 (0.50–1.16)	0.76 (0.49–1.16)
11–20 cigarettes/day	97	13,205.8	0.70 (0.52–0.93)	0.66 (0.49–0.89)
21–30 cigarettes/day	67	8,473.8	0.64 (0.46–0.87)	0.60 (0.43–0.83)
>30 cigarettes/day	27	3,518.2	0.61 (0.40–0.94)	0.60 (0.39–0.92)
p for trend			0.003	0.002
≤20 years of smoking	54	4,791.9	0.64 (0.45–0.92)	0.62 (0.43–0.89)
21–30 years of smoking	106	11,477.1	0.71 (0.53–0.94)	0.68 (0.51–0.91)
31–40 years of smoking	46	7,909.8	0.74 (0.51–1.06)	0.70 (0.48–1.01)
>41 years of smoking	10	4,623.5	0.39 (0.20–0.77)	0.36 (0.18–0.73)
p for trend			0.001	0.001
<i>Women</i>				
Never	474	51,995.6	1.00	
Former	29	2,841.7	0.91 (0.63–1.33)	0.91 (0.62–1.33)
Current	45	6,305.6	0.65 (0.47–0.88)	0.64 (0.47–0.88)
≤10 cigarettes/day	24	3,172.4	0.70 (0.46–1.06)	0.72 (0.47–1.08)
>10 cigarettes/day	21	3,044.7	0.61 (0.39–0.94)	0.58 (0.37–0.91)
p for trend			0.007	0.005
≤20 years of smoking	33	3,986.7	0.64 (0.45–0.92)	0.63 (0.44–0.90)
>20 years of smoking	11	2,256.6	0.62 (0.34–1.14)	0.64 (0.35–1.16)
p for trend			0.003	0.003

¹ Adjusted for age, marital status, years of education, body mass index, occupational history of farming, and alcohol intake.

Table 4. Risk of cedar pollinosis according to change in smoking status during the follow-up

	Cases	Subjects	Odds ratio (95%CI)	
			age-adjusted	multivariate ¹
<i>Men</i>				
Never to never	88	916	1.00	
Never to current/former	0	4	0.00	
Former to former	133	1,592	0.97 (0.73–1.30)	0.94 (0.70–1.26)
Current to former	70	820	0.93 (0.66–1.29)	0.88 (0.63–1.24)
Former to current	8	95	0.75 (0.35–1.61)	0.74 (0.35–1.60)
Current to current	148	2,254	0.57 (0.43–0.75)	0.55 (0.41–0.73)
<i>Women</i>				
Never to never	471	5,484	1.00	
Never to current/former	0	26	0.00	
Former to former	22	228	0.97 (0.62–1.54)	0.98 (0.61–1.57)
Current to former	14	196	0.82 (0.47–1.43)	0.75 (0.42–1.34)
Former to current	6	75	0.62 (0.27–1.45)	0.61 (0.26–1.42)
Current to current	29	463	0.53 (0.36–0.79)	0.53 (0.36–0.79)

¹ Adjusted for age, marital status, years of education, body mass index, occupational history of farming, and alcohol intake.

posure including metal, chemicals, plastics, woods, and oils, and menstrual and reproductive histories (women only) did not alter the results substantially (data not shown).

Table 4 shows the ORs of cedar pollinosis according to any change in smoking status during the follow-up period. In both men and women, a significantly decreased risk was observed among those who continued to smoke in comparison with those who remained to be never smokers. There was no risk increase among those who had quit smoking during the follow-up. A moderately decreased risk was observed among individuals who had resumed smoking, although the reduction was not statistically significant.

A total of 191 participants with cedar pollinosis (156 men and 35 women) had been smokers at the onset of the disease. Of that group, no men and two women had quit smoking after the onset of the disease during the follow-up period.

Sensitivity analysis excluding those who had reported histories of allergic diseases at baseline or those who reported incidence within the first 3 years of follow-up revealed that the results were essentially unaltered (table 5). Changing the definition of cedar pollinosis to one including four symptoms occurring during spring did not substantially alter the results either.

Discussion

In this follow-up, we found that smoking was significantly inversely associated with the risk of cedar pollinosis. There was a dose-response relationship between the intensity of smoking and the risk of cedar pollen allergy. A potential limitation of this study is that the information of smoking status was obtained at the baseline but the identification of cases was based on the follow-up questionnaire. Clearly it would be better if we knew that subjects were non-cases by administering the questionnaire at baseline. However, when this bias due to misclassification of disease status was evaluated by reanalyzing data after excluding those who had reported allergies at the baseline or after changing the inclusion criteria for cases, the results were similar. It is also possible that the presence of signs related to cedar pollinosis may have affected the status of smoking. In such cases, smokers who developed the symptoms would be more likely to quit smoking. However, there was no risk increase for former smokers at the baseline as well as for those who quit smoking during the follow-up. In addition, only a few individuals quit smoking after contracting cedar pollinosis during the follow-up period. The finding of a lower risk of cedar pollinosis in those who took up smoking again in comparison with those who did not smoke during the follow-up was consistent with the interpretation of a protective

effect of smoking, although the risk reduction was not statistically significant. Nonetheless, we cannot exclude the possibility that smokers are less likely to report the symptoms because they are thought to be less health conscious than non-smokers. It is also possible that smokers are less likely to perceive the seasonality of the symptoms.

Studies on smoking and allergic diseases have yielded conflicting results. Exposure to environmental tobacco smoke in children has been associated with asthma [9]. However, the role of active smoking in adults for the etiology of asthma is unclear, although it is known that smoking is associated with worsening of symptoms and an accelerated decline in lung function [9]. Among studies on smoking and allergic rhinitis/sino-conjunctivitis, some studies have suggested a protective effect of smoking [10–13]. No association [5, 14–16] as well as a positive association [17, 18] between smoking and allergic rhinitis has also been reported. An increased risk of allergic rhinitis among former but not current smokers has been reported [19]. These studies were all cross-sectional. Prospective studies have supported findings of an inverse association between smoking and allergic rhinitis. In a prospective study of 1,370 subjects, there was a tendency for non-smokers to be more likely to experience the onset of allergic rhinitis [20]. In a cohort study of 191 men seen 5 years apart, allergic rhinitis was positively associated with ex-smokers and inversely associated with current smoking [21]. The risk of developing allergic sensitization to aeroallergens was lower among sustained smokers than never smokers in a prospective study of 734 subjects [22].

Tobacco smoke has been shown to have a suppressive effect on human immunity, including an inhibitory effect on cytokine production [23], depression of immunoglobulin levels [24] and depression of T-cell responsiveness [25]. The immunosuppressive effect of smoking may partially explain the results observed in our study. The process of activation of the T cell is specific to an allergen. The effect of smoking may differ in different groups of allergens, which may be related to the inconsistent results among previous studies on smoking and allergic rhinitis. Smokers have been found to have greater serum concentrations of total IgE, but the association between smoking and sensitization to environmental allergens is different for different allergens [26].

The limitation of the diagnosis of the cedar pollinosis based on self-reporting of the symptoms should be considered. The specificity was not high in the present study. However, our reanalysis showed that the relationship be-

Table 5. Sensitivity analyses: risk of cedar pollinosis according to smoking at baseline

	Hazard ratio ¹ (95% CI)	
	men	women
Excluding those who had reported histories of allergic diseases at baseline		
Never	1.00	1.00
Former	0.97 (0.74–1.28)	0.98 (0.66–1.44)
Current	0.63 (0.49–0.81)	0.64 (0.47–0.89)
Excluding those who reported incidence within the first 3 years of follow-up		
Never	1.00	1.00
Former	0.96 (0.68–1.34)	0.78 (0.47–1.29)
Current	0.68 (0.49–0.93)	0.67 (0.46–0.98)
Incidence with all four symptoms occurred during spring		
Never	1.00	1.00
Former	1.01 (0.65–1.56)	0.92 (0.50–1.71)
Current	0.64 (0.43–0.97)	0.58 (0.34–1.01)

¹ Adjusted for age, marital status, years of education, body mass index, occupational history of farming, and alcohol intake.

tween smoking and the risk of cedar pollinosis was essentially the same even after we adopted a definition with low sensitivity and high specificity. The measurement of pollen-specific IgE is desirable for determining the presence of cedar pollinosis. However, it is not practical for the follow-up of a large number of subjects, as in our study. Most of the previous large-scale population-based studies on the risk factors of allergic rhinitis among adults have been based on self-administered questionnaire [13, 17–19].

The response rate was not very high in the present study. In addition, the lack of information on pollen allergy status among subjects who had died or moved should also be considered. However, it is unlikely that smokers who did not participate in the follow-up study were more likely to be affected by cedar pollinosis than smokers who had participated in the study. Similarly, it is unlikely that smoking was positively associated with the risk of pollen allergy among those who had died or moved.

We could not obtain information on the family history of pollen pollinosis or other allergic diseases, which may have a confounding effect. Genetic predisposition may be associated with smoking status. However, in the present study, only a few individuals quit smoking after the onset of cedar pollinosis. It is unlikely that recognizing the history of cedar pollinosis or allergic diseases

among families will substantially affect individual's tobacco smoke. In addition, information obtained from the self-reporting of families' non-serious diseases, such as allergies, would not be sufficiently accurate. Nonetheless, we cannot rule out the possibility that unmeasured or unknown confounding factors accounted for the associations observed in our study.

We found that smoking was significantly inversely associated with cedar pollinosis. There is no reason to change tobacco policies. Because of the toxicity and carcinogenic nature of tobacco products, they should not be used therapeutically. However, some components of tobacco

may protect against cedar pollinosis. Our finding could provide clues about therapeutic strategies for protection against cedar pollinosis. The results from the present study also encourage a more intensive evaluation of the relationship between smoking and allergic rhinitis.

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