3) 長期管理におけるFeNOの有用性（表2）

気道炎症の鎮静化を目的とする長期管理において，気道炎症のバイオマーカーと考えられるFeNOを指標としてICSの投与量を調節することは理にかなった治療戦略と考えられる．Pijnenburgらは，6～18歳の喘息児を臨床症状とFeNOを参考にICSの投与量を調節する群と臨床症状のみでICSの投与量を調節する対照群に分けて1年間経過をみたところ，前者では気道過敏性とFEV_1の改善が後者に比して有意であり，かつICSの投与量は両群間で有意差はなかったと報告している[13]．しかし，Fritschらが同年齢の子どもたちを対象に同様な検討を6カ月間行った結果，両群間に喘息のコントロール状態に差はなく，FeNO群で有意にICSの使用量が対照群に比して多かったと報告している[14]．さらに，Szeflerらが12～18歳を対象に46週間の検討を行った結果でも両群間で効果に差はなく，むしろFeNO群におけるICSの投与量は対照群に比してフルチカゾン換算で平均119μg/日多かった[15]．一方，これらの方法は医療機関を受診した際のFeNOのみを参考にしていたため，de Jongsteらは自宅に携帯型のFeNO測定器機を設置し，日々のFeNOを喘息症状や発作時治療薬の使用状況などと共にテレモニタリングして6～18歳の喘息児を対象に上記と同様の検討を30週間行ったが，FeNOを通常のモニタリングに追加してICSの投与量を調節する意義は認められなかったと報告している[16]．そして，これら4つの結果をメタ解析した結果でも，日常診療においてFeNOを指標としてICSの投与量を調節することは推奨されないと結論づけている[17]．

このように期待通りの結果が出なかった理由のひとつとして，ステロイドはNO産生酵素の誘導を直接抑制する[18]ため，必ずしも好酸球性炎症を十分に抑制していなくてもICS投与によってFeNOが低下することが考えられる．事実，中等症～重症の喘息児において，FeNOは生検によって調べた気道上皮下の好酸球数とは相関が認められなかったとの報告がある[19]．さらに，ICS使用中の喘息児では，喘息のコントロール状態とFeNOは相関しないことも示されている[20][21]．

上記のように，長期管理中のICS投与量を調節する際に臨床症状や肺機能の結果に加えてFeNOを加えることのメリットはなさそうであるが，ICSを終了する際の目安にはなる可能性が示されている．Pijnenburgらはコントロール良好な小児においてICSを中止しFeNOを経時的に測定したところ，ICS中止後24週間以内に喘息症状の再燃を認めた群では，再燃を認めなかった群に比してICS中止後2週と4週のFeNOが有意に上昇しており，さらにICS中止後4週のFeNOが49 ppbをカットオフ値とすると，ICS中止後の喘息症状の再燃を予測する感度は71%，特異度は93%であったと報告している[22]．また，我々のFeNOを定期的に測定した後方視的検討では，コントロール状態が良好であってもFeNOが上昇傾向にある時に長期管理薬（ICSあるいはLTRA）をステップダウンすると，その後に再燃しやすいことが示されている[23]．さらに，FeNOの上昇は，治療へのアドヒアランス(服薬状況や吸入手技など)低下[24]やアレルゲン曝露の増加[25]の指標となることが示されており，FeNOを繰り返し測定することの臨床的意義は大きい．最近では，自宅でFeNOを毎日モニタリングし，その値の変動が症状や重症度，さらには発作予測に活用できる可能性も示されているが[26][27]，実際の臨床での有用性については費用対効果を含め，さらなる検討が必要である．

4) FeNOの問題点と今後の方向性

以上述べてきたように，FeNOは気道の好酸球炎症のバイオマーカーとして現時点における最良のものであるが，FeNOは種々の因子によって影響をうけるため，実際の臨床では，FeNOのみを単独の指標とするのではなく，臨床症状や肺機能など他の因子を含めた総合判断が必要である．また，FeNOを経時的に測定することによって，患児の状態の変化（治療へのアドヒアランスも含め）を早期にピックアップできる可能性があり，その限界を理解した上での活用であれば，FeNO測定の臨床的意義は極めて高い．しかし，その測定には正確さが求められ[28]，また低年齢児での測定には

表3　呼気凝縮液中のバイオマーカー

・酸化ストレス	・炎症
—H_2O_2	—pH
—8-isoprostane	—アラキドン酸代謝物
—Malondialdehyde	・プロスタグランジン
・窒素化ストレス	—PGE_2, $PGF_{2\alpha}$, TXB_2
—Nitrite	・ロイコトリエン
—Nitrate	—CysLT（LTC_4, LTE_4, LTD_4）
—Nitrotyrosine	—LTB_4
—Nitrosothiol	—サイトカイン
	・IL-1β, IL-4, IL-8, IL-17, TNF-α, TGF-β
	—ケモカイン
	・RANTES, IP-10, MDC, eotaxin

工夫も必要である[29)30)]．さらに，気道狭窄のある場合にはFeNOが低下する場合があり[31)]，結果の解釈には注意を要する．

最近，より精度の高い測定方法として気道の末梢側と中枢側のFeNOを測定する方法が開発され[32)]，小児領域でもその臨床的意義について知見が得られはじめている[33)34)]．

呼気凝縮液

呼気を冷気の中を通すことによって得られる呼気凝縮液（exhaled breath condensate, EBC）中にはバイオマーカーとなり得る種々の物質が存在し，それらは酸化ストレス，窒素化ストレス，その他の炎症を反映するものに大別される[35)]（**表3**）．その中でもLTE_4は，FeNOに比べICS使用による影響が少なく[36)]，気管支上皮基底膜の肥厚の程度と有意な相関があるとの報告もあり[37)]，FeNOでは測定できない病態を反映している可能性がある．また，Robroeksらは，喘息児を含む小児（平均10歳）におけるFeNOならびにEBC中の各種物質（nitrite, nitrate, H_2O_2, 8-isoprostane, IFN-γ, TNF-α, IL-4, IL-5, IL-10, pH）を測定し，喘息の診断マーカーとしてはEBC中のIL-4のみが，一方喘息のコントロール状態のマーカーとしてはFeNOとEBC中の8-isoprostane, IFN-γ, IL-4が，さらに喘息の重症度の指標としてはFeNOとEBC中の8-isoprostane, nitrite, nitrateが有意であったと報告し[38)]，それぞれの目的によってバイオマーカーを使い分ける必要があることを示している．しかし，EBCを採取するにはある程度の時間がかかり，さらにこれらの物質を簡便に測定できる器機がないため，現時点ではこれらの物質を日常診療におけるバイオマーカーとして活用することは困難である．

これからのバイオマーカー

今までの方法では測定するものを基本病態から類推し限定して測定していたが，最近ではEBC中の物質を網羅的に測定し，どのような物質が関与しているかを解析するメタボロミックス（metabolomics）が用いられるようになってきている．Carraroらは，重症喘息児，非重症な喘息児，対照群の3群（8～17歳）におけるEBCを高速液体クロマトグラフィーとマススペクトロメーターをつないだシステムで解析し，各種代謝産物の濃度の違いによって3群が判別できること，さらにそれらにはレチノイン酸，アデノシン，ビタミンDなどアレルギーと関係のある物質が含まれていることを示している[39)]．また，呼気の揮発物質（volatile organic compound）についても同様な解析方法を用いた研究が行われている．van de Kantらは，喘鳴を繰り返す2～4歳児ならびに対照群の呼気をガスクロマトグラフィーとマススペクトロメーターをつないだシステムで解析し，両者を鑑別するのに有効であったと報告している[40)]．このなかでも特に呼気分析は乳幼児であっても呼気の

採取が比較的容易であるため，今後の開発が期待される．

おわりに

FeNOは，小児喘息の日常診療において有用なバイオマーカーである．本邦でも既に外来で簡便に測定できる器機が入手可能な状態であり，一日も早く保健適応されることが望まれる．一方，FeNOは好酸球性炎症という喘息の一側面をみているにすぎないため，今後メタボロミックスの手法を用いて，EBCや呼気の分析がさらに発展することが期待される．

利益相反（conflict of interest）に関する開示：著者は本論文の研究内容について他者との利害関係を有しません．

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気管支喘息(小児)のバイオマーカーに関する問題

2-1. 小児において，FeNO を低下させる因子は何か．

a 高年齢

b アレルギー体質

c アレルギー性鼻炎

d 受動喫煙

e アレルゲン曝露

専門医のためのアレルギー学講座問題の解答

第13回 バイオマーカー

「2. 気管支喘息(小児)のバイオマーカー」：足立雄一

2-1. 正解 d

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ORIGINAL ARTICLE | EPIDEMIOLOGY AND GENETICS

Cedar and cypress pollen counts are associated with the prevalence of allergic diseases in Japanese schoolchildren

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asthma; children; conjunctivitis; pollen; rhinitis.

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Abstract

Background: Patients allergic to pollen have been known to become more symptomatic during pollen season compared with the nonpollen season. However, there are few studies regarding whether higher exposure to pollen might increase the prevalence of allergic diseases.

Methods: An ecological analysis was conducted to evaluate whether pollen exposure is associated with the prevalence of allergic diseases in schoolchildren. Pollen count data of Japanese cedar (*Cryptomeria japonica*) and Japanese cypress (*Chamaecyparis obtusa*), which are the major pollen allergens in Japan, were obtained from each prefecture. The prevalence of allergic diseases in schoolchildren in each prefecture was based on a nationwide cross-sectional survey using the International Study of Asthma and Allergies in Childhood questionnaire.

Results: After omitting three prefectures where pollen data were not available, data of 44 prefectures were analysed. The prevalence of allergic rhinoconjunctivitis in children aged 6–7 years was positively associated with both cedar and cypress pollen counts ($P = 0.01$, both), whereas the prevalence of allergic rhinoconjunctivitis in children aged 13–14 years was positively associated with only cypress pollen counts ($P = 0.003$). Furthermore, the prevalence of asthma was positively associated with cedar pollen counts in 6- to 7-year-old children ($P = 0.003$) but not cypress pollen counts in either age group.

Conclusions: There are ecological associations between pollen counts and the prevalence of allergic diseases in Japanese schoolchildren. Further studies are needed to determine whether the difference between the effects of cedar and cypress pollens is attributable to pollen counts or allergenicity.

Asthma and allergic rhinitis are the most common chronic diseases in childhood and impair the quality of life of the patients and their family (1, 2). The incidence of both disorders has increased dramatically worldwide in the last few decades (3). However, the prevalence of allergic diseases varies widely throughout the world. The International Study of Asthma and Allergies in Childhood (ISAAC) showed that the prevalence of asthma and allergic rhinoconjunctivitis varies 20- to 40-fold in the world (4, 5).

Pollens, along with climate and air pollutants, are among the environmental factors hypothesized to contribute to this variation (6). In patients with allergic rhinitis, symptoms become more frequent and more severe when pollen counts increase (7, 8). Furthermore, patients with asthma require attendance at emergency departments and hospital admissions more frequently when the airborne pollen concentration is higher (9–12).

However, there are only a few studies evaluating the ecological associations between pollen counts and the prevalence of allergic diseases, and the results were inconsistent. Studies comparing the prevalence of allergic diseases between an area with higher pollen count and another with low pollen count showed that higher exposure to pollen was associated with a higher sensitization rate in children (13) and prevalence of allergic rhinitis in adults (14, 15). By contrast, a large study performed in 28 centres within 11 countries showed that there was little relationship between pollen exposure and the prevalence of allergic symptoms in children (16). This inconsistency may be attributable to geographical differences in the major pollen species and lifestyles of the study subjects. Ecological studies to evaluate this association for specific pollen exposure in a large homogeneous population are warranted.

Therefore, we performed an ecological analysis to evaluate whether there were associations between specific pollen counts (Japanese cedar and Japanese cypress) and the prevalence of allergic diseases in Japanese schoolchildren, using data on pollen counts and the prevalence of allergic diseases in each prefecture throughout Japan.

Methods

Study participants

The prevalence of allergic diseases in children aged 6–7 and 13–14 years in each prefecture was based on the data of a nationwide survey that was conducted throughout Japan in 2008; details of the methods and response rates have already been published (17). In this survey, samples were randomly selected from all prefectures ($n = 47$) in Japan using public schools as the sampling units because more than 95% of schoolchildren attend public schools in Japan.

Questionnaire

The survey used the Japanese version of the written questionnaire of ISAAC, which was distributed by teachers at the participating schools (17). The responses to the questions were reported by parents for children aged 6–7 years and were self-reported for children aged 13–14 years.

Allergic rhinoconjunctivitis was defined as positive answers to both of these questions: 'In the past 12 months, have you (has your child) had a problem with sneezing, or a runny, or blocked nose when you (he/she) did not have a cold or the flu?' and 'In the past 12 months, has this nose problem been accompanied by itchy-watery eyes?' Asthma was defined as a positive answer to the question: 'Have you (has your child) had wheezing or whistling in the chest in the past 12 months?'

Pollen and meteorological data

Japanese cedar (*Cryptomeria japonica*, family Taxodiaceae) and Japanese cypress (*Chamaecyparis obtusa*, family Cupressaceae) are the major causes of pollinosis in Japan. We used pollen data from the Association of Pollen Information in Japan. The cedar and cypress pollen counts were measured at observation facilities located in all prefectures except for Okinawa. Because a Durham's sampler has been the most popular apparatus for measuring pollen counts in Japan, we omitted data from two prefectures in which the pollen counts were measured by different methods. The data from these three prefectures were excluded, and the data from the 44 remaining prefectures included in the final analysis. The average values of the pollen counts per year over the past 4 years were used in this study because it may take time for children to become sensitized and develop allergic symptoms (8, 18). Meteorological data were obtained from the Japan Meteorological Agency (http://www.jma.go.jp/jma/indexe.html). The mean annual temperature and relative humidity measured at each prefectural capital in 2008 were used in this analysis.

Statistical analyses

Chi-square tests were used to assess whether the prevalence of allergic diseases differed between children included in this study and those who were excluded. The data for the two types of tree pollen and the two age groups were analysed separately. Associations between pollen counts and the prevalence of allergic rhinoconjunctivitis were determined using Pearson's product-moment correlation coefficient. Multivariable regression analyses of the associations between pollen counts and the prevalence of allergic symptoms were adjusted for the gender ratio (17), mean annual temperature (19) and mean annual relative humidity (19). The associations were analysed after adjustment for the pollen counts of other species as potential confounders, as cross-reactivity exists between cedar and cypress pollens (20). The prevalence of allergic rhinoconjunctivitis was included as a confounder in the analyses of the associations between pollen counts and the prevalence of asthma because allergic rhinitis may affect asthma patients (21, 22). P values <0.05 were considered to indicate statistical significance. All analyses were performed using the statistical package 'SPSS for Windows version 19' (SPSS Inc., Chicago, IL, USA).

Ethics

The study protocol was approved by the independent review board of the National Center for Child Health and Development.

Results

Data were analysed in 44 prefectures, in which cedar and cypress pollen counts were measured separately, including 40 975 children aged 6–7 years and 45 787 children aged 13–14 years. The average values of cedar and cypress pollen counts in the 44 prefectures analysed were 2967 counts/cm^2 (range, 34–7912 counts/cm^2) and 1245 counts/cm^2 (range, 1–6048 counts/cm^2), respectively. Cedar pollen counts were higher in prefectures in eastern Japan (Fig. 1A), and cypress pollen counts were higher in prefectures on the Pacific side than along the Sea of Japan (Fig. 1B).

There was a wide range of the prevalence of allergic rhinoconjunctivitis (range, 8.1–29.2%) and asthma (range, 9.4–17.3%) between prefectures in the 6- to 7-year-old children. Similar to the 6- to 7-year-old children, the prevalence of allergic rhinoconjunctivitis ranged from 10.8% to 30.9% and that of asthma ranged from 6.1% to 13.2% in the 13- to 14-year-old children. The prevalence of allergic rhinoconjunctivitis in 6- to 7-year-old children was higher in prefectures in

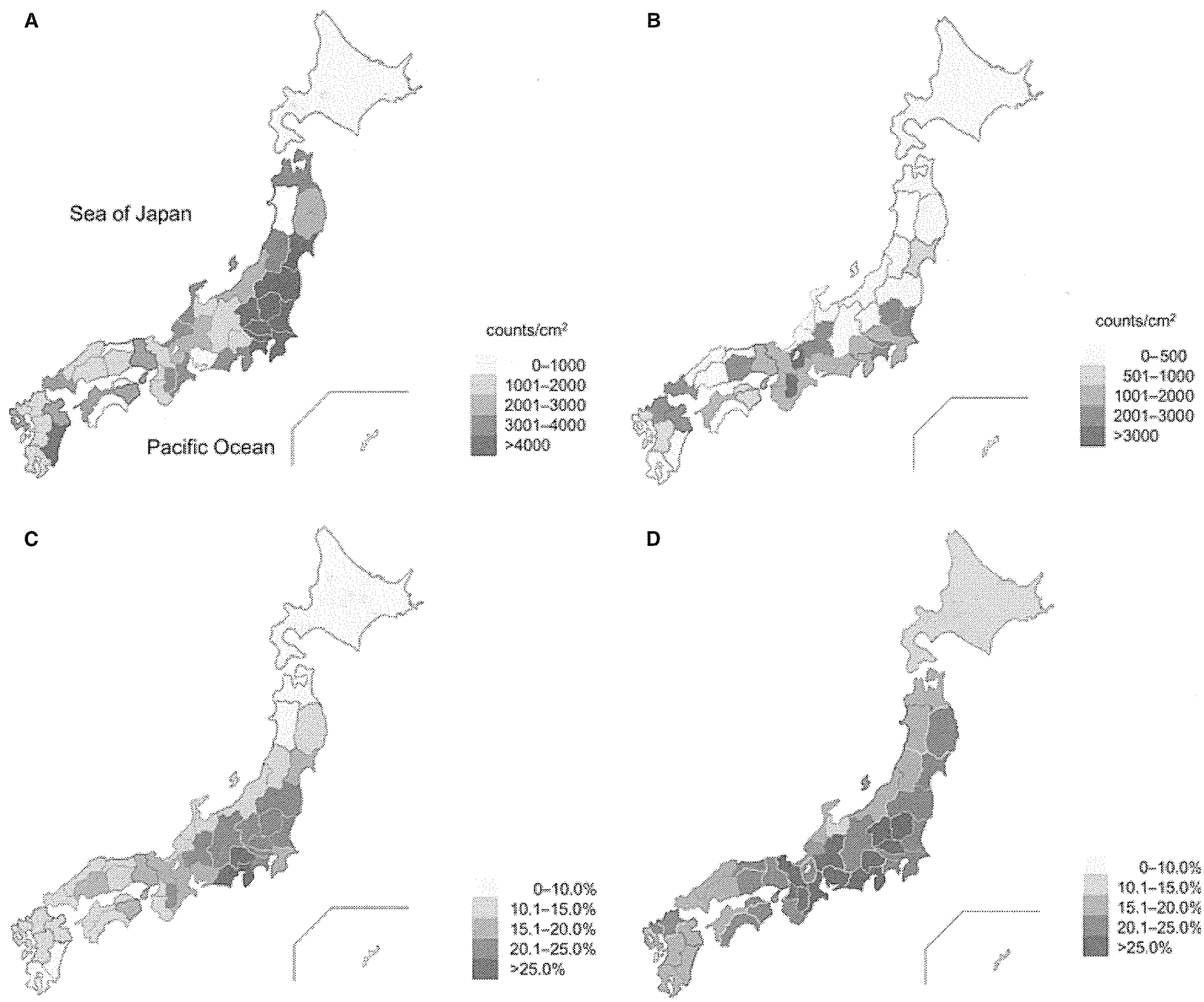

Figure 1 Maps of pollen counts and the prevalence of allergic rhinoconjunctivitis in Japan. (A) Japanese cedar pollen counts. (B) Japanese cypress pollen counts. (C) The prevalence of allergic rhinoconjunctivitis in 6- to 7-year-old children. (D) The prevalence of allergic rhinoconjunctivitis in 13- to 14-year-old children.

eastern Japan (Fig. 1C), whereas the prevalence of allergic rhinoconjunctivitis in 13- to 14-year-old children was higher in prefectures on the Pacific side of eastern and central Japan (Fig. 1D). Cedar pollen counts were positively associated with the prevalence of allergic rhinoconjunctivitis in 6- to 7-year-old children ($R = 0.48$, $P = 0.001$) (Fig. 2A) but not in 13- to 14-year-old children ($R = 0.18$, $P = 0.24$) (Fig. 2B). Cypress pollen counts were positively associated with the prevalence of allergic rhinoconjunctivitis in 6- to 7-year-old children ($R = 0.43$, $P = 0.004$) and 13- to 14-year-old children ($R = 0.47$, $P = 0.001$) (Fig. 2C,D). Even after adjustment for confounders, the prevalence of allergic rhinoconjunctivitis remained positively associated with cedar pollen counts for the 6- to 7-year-old children ($P = 0.01$) and cypress pollen counts for both the 6- to 7-year-old children and 13- to 14-year-old children ($P = 0.01$ and $P = 0.003$, respectively) (Table 1). Cedar pollen counts were not associated with the prevalence of allergic rhinoconjunctivitis in 13- to 14-year-old children after adjustment for confounders ($P = 0.29$).

In general, the prevalence of allergic rhinoconjunctivitis was higher in 13- to 14-year-old children than in 6- to 7-year-old children. However, the difference between the two age groups was inversely associated with the prevalence of allergic rhinoconjunctivitis in the younger children ($R = -0.52$, $P < 0.001$) (Fig. 3A). Therefore, we analysed the association between the pollen counts and the differences in the prevalence of allergic rhinoconjunctivitis between the two age groups. Differences in the prevalence of allergic rhinoconjunctivitis were inversely associated with cedar pollen counts ($R = -0.50$, $P = 0.001$) (Fig. 3B) but not with cypress pollen counts ($R = -0.28$, $P = 0.86$) (Fig. 3C).

We next analysed the associations between pollen counts and the prevalence of asthma (Table 1). After adjustment for

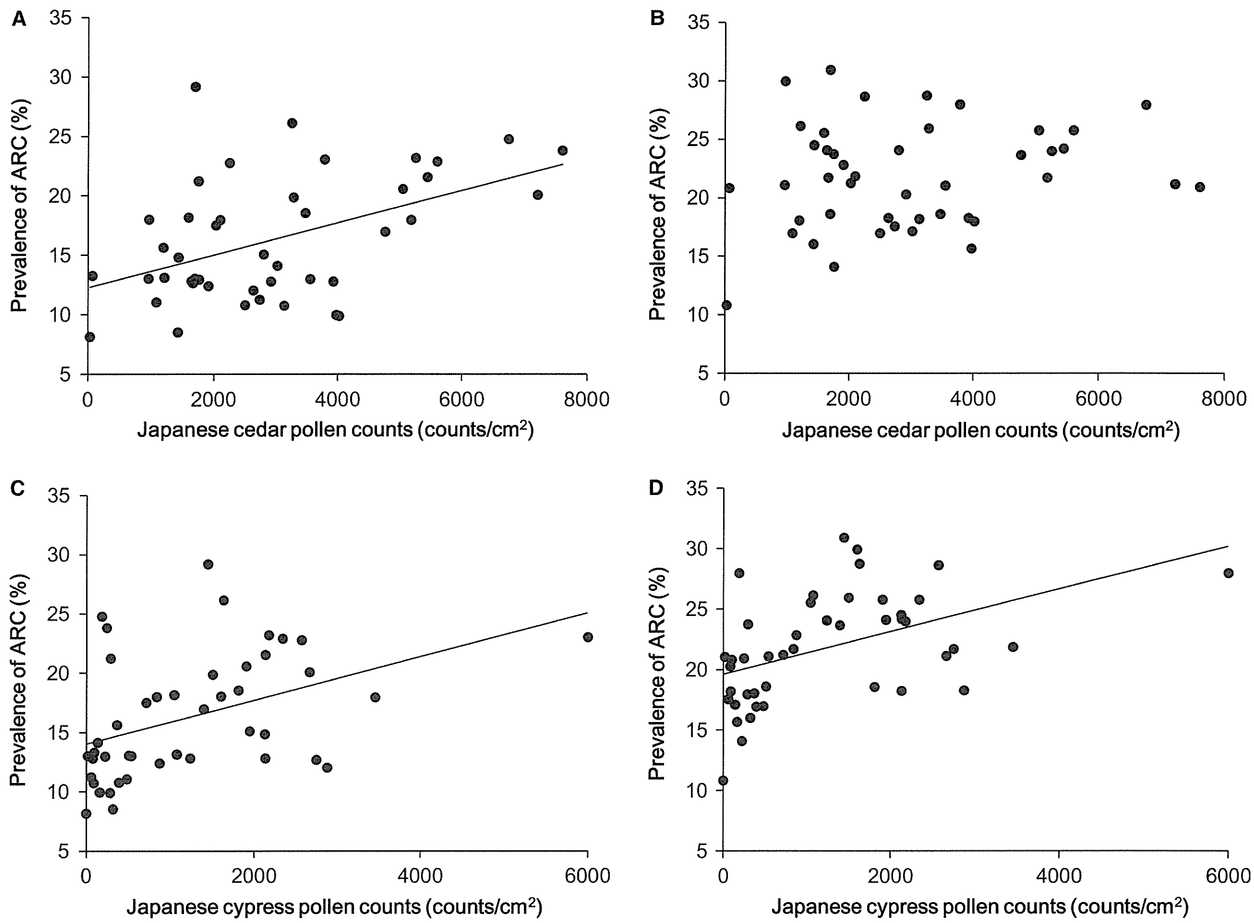

Figure 2 Pollen counts and the prevalence of allergic rhinoconjunctivitis (ARC). (A) Positive association between cedar pollen counts and the prevalence of ARC in 6- to 7-year-old children ($R = 0.48$, $P = 0.001$). (B) No association between cedar pollen counts and the prevalence of ARC in 13- to 14-year-old children ($R = 0.18$, $P = 0.24$). (C) Positive association between cypress pollen counts and the prevalence of ARC in 6- to 7-year-old children ($R = 0.43$, $P = 0.004$). (D) Positive association between cypress pollen counts and the prevalence of ARC in 13- to 14-year-old children ($R = 0.47$, $P = 0.001$).

confounders, cedar pollen counts were positively associated with the prevalence of asthma in 6- to 7-year-old children ($P = 0.003$) but not in 13- to 14-year-old children ($P = 0.46$). Cypress pollen counts were not associated with the prevalence of asthma in either age group ($P = 0.07$ for the 6- to 7-year-old children and $P = 0.89$ for the 13- to 14-year-old children).

Discussion

In this ecological study, we found a positive association between cedar and cypress pollen counts and the prevalence of allergic rhinoconjunctivitis and asthma in Japanese schoolchildren. Consistent with our finding, a study performed in Italian children aged 11–14 years revealed that children living in a high-pollen-count area showed a significantly higher percentage of sensitization to pollens than those in another area with low pollen counts (13). Similar results were shown in French adults (15) and the genetically homogeneous Inuit population (14), although their sample sizes were small. By contrast, an ecological study performed in 11 countries (9 European countries, Australia and Kuwait) revealed that there was little relationship between pollen exposure and the prevalence of allergic symptoms in children aged 13–14 years (16). Inconsistency with our results might be explained by the geographical heterogeneity in the lifestyle of the study subjects (23, 24) and the prevalence of plant species and their related allergens (25).

Cedar pollen counts were positively associated with the prevalence of allergic rhinoconjunctivitis in 6- to 7-year-old children but not in 13- to 14-year-old children. Although the prevalence of allergic rhinoconjunctivitis is generally higher in 13- to 14-year-old children than in 6- to 7-year-old children (5), the differences in the prevalence of allergic rhinoconjunctivitis between the two age groups were inversely associated with the cedar pollen counts. A retrospective analysis performed in the United States revealed that over 50% of children with allergic rhinitis were sensitized to at least one pollen by the age of 3 years and that the sensitization rate increased with age and plateaued by the age of 8 years (18). Together with our results, it is suggested that children in areas heavily exposed to cedar pollen might be sensitized to cedar pollen in early childhood, and the prevalence of allergic rhinoconjunctivitis might therefore plateau by the age of 6–7 years. By contrast, the prevalence of allergic rhinoconjunctivitis in less-exposed areas might not yet have plateaued by the age of 6–7 years and might thus continue to increase thereafter. Consequently, cedar pollen counts were not associated with the prevalence of allergic rhinoconjunctivitis in 13- to 14-year-old children.

Table 1 Associations between pollen counts and the prevalence of allergic diseases

	Japanese cedar		Japanese cypress	
	Coefficient (SE)	*P*-value	Coefficient (SE)	*P*-value
Allergic rhinoconjunctivitis				
6- to 7-year-old children	1.07 (0.39)*	0.01	1.49 (0.57)†	0.01
13- to 14-year-old children	0.34 (0.32)*	0.29	1.52 (0.49)†	0.003
Asthma				
6- to 7-year-old children	0.49 (0.16)‡	0.003	−0.43 (0.23)§	0.07
13- to 14-year-old children	0.11 (0.15)‡	0.46	0.04 (0.30)§	0.89

SE, standard error.
Coefficient is for each pollen count increment of 1000 counts/cm^2.
*Adjusted for the gender ratio, mean annual temperature, mean annual relative humidity, and cypress pollen counts.
†Adjusted for the gender ratio, mean annual temperature, mean annual relative humidity, and cedar pollen counts.
‡Adjusted for the gender ratio, mean annual temperature, mean annual relative humidity, cypress pollen counts, and prevalence of allergic rhinoconjunctivitis.
§Adjusted for the gender ratio, mean annual temperature, mean annual relative humidity, cedar pollen counts, and prevalence of allergic rhinoconjunctivitis.

Unlike cedar pollen counts, cypress pollen counts were positively associated with the prevalence of allergic rhinoconjunctivitis in 6- to 7-year-old children, and this positive association persisted in 13- to 14-year-old children. In Japan, cedar pollen counts are usually more than twice those of cypress. Therefore, the prevalence of allergic rhinoconjunctivitis due to cypress pollen might require additional time to reach a plateau than that caused by cedar pollen. The discrepancy between the results for cedar and cypress pollens may be attributable not only to differences in pollen counts but also to differences in antigenicity. T-cell reactivity differs between cedar and cypress pollens (26, 27), although there is some cross-reactivity (20).

Cedar pollen counts were positively associated with the prevalence of asthma in 6- to 7-year-old children even after adjustment for confounders, including the prevalence of allergic rhinoconjunctivitis. Pollens may induce asthma symptoms independently of allergic rhinitis by two mechanisms. The first is inhalation of pollen allergens. Pollen grains are generally too large to penetrate the lower airway and thus do not provoke asthma symptoms. However, small particles of cedar pollen contain a major pollen allergen (Cry j 1) (28) and are likely to induce an asthma attack (29). The second is that pollens may act as adjuvants to exacerbate asthmatic symptoms. Intranasal administration of ovalbumin with cedar pollen induced ovalbumin-specific IgE responses, although the administration of ovalbumin alone did not induce the production of ovalbumin-specific IgE (30). Cedar pollen may thus enhance sensitization to other allergens as well as pollen itself and thereby influence asthma in young children. The prevalence of asthma was not associated with cypress pollen counts. The reason for this discrepancy between cedar and cypress pollens remains unclear and warrants further investigation.

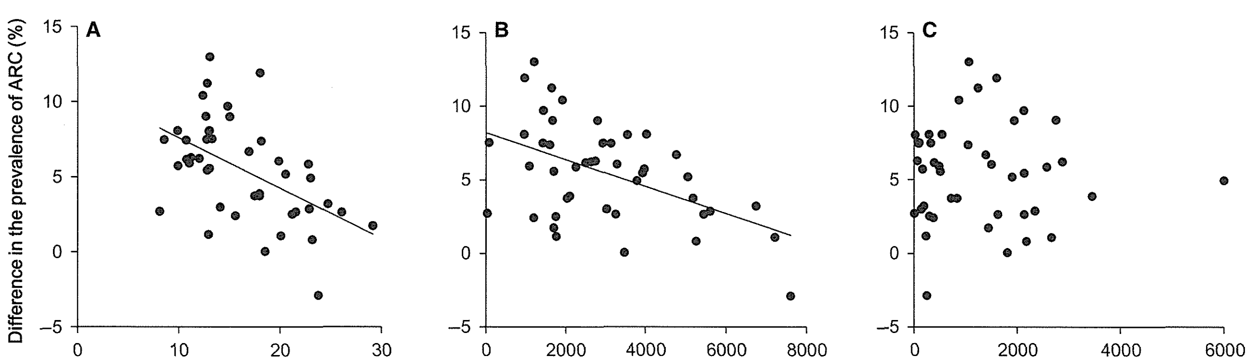

Figure 3 Differences in the prevalence of allergic rhinoconjunctivitis (ARC) between 6- to 7-year-old children and 13- to 14-year-old children. (A) Inverse association between the prevalence of ARC in 6- to 7-year-old children and the difference in the prevalence of ARC between the two age groups ($R = -0.52$, $P < 0.001$). (B) Inverse association between cedar pollen counts and the difference in the prevalence of ARC between the two age groups ($R = -0.50$, $P = 0.001$). (C) No association between cypress pollen counts and the difference in the prevalence of ARC between the two age groups ($R = -0.03$, $P = 0.86$).

The strength of our study is that it addresses the associations between two types of tree pollen and the prevalence of allergic diseases in children in two different age groups. One limitation is that our study was a questionnaire-based survey without testing for sensitization. Estimation of the prevalence of allergic rhinoconjunctivitis by a questionnaire only may be not very sensitive in young children (31). However, sensitization to any allergen is strongly associated with allergic rhinoconjunctivitis as assessed by the ISAAC questionnaire (32), and this questionnaire has previously been used for ecological analyses (6, 16). Another limitation is that we did not adjust our analysis for the levels of air pollutants, such as SPM, SO_2 and NO_X. Air pollutants can affect both allergic subjects (33) and the allergenicity of pollens (34). The levels of these pollutants have been reported to be affected by the distance from major roads and the traffic count (35) and vary widely even within the same prefecture. Therefore, we did not include air pollutants as confounders in this analysis.

In conclusion, pollen counts of cedar and cypress are positively associated with the prevalence of allergic rhinoconjunctivitis and asthma in Japanese schoolchildren. Although both cedar and cypress pollens are tree pollens, they show different effects regarding the prevalence of allergic diseases. Further studies are required to elucidate the reason for this discrepancy.

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Author contributions

Koichi Yoshida analysed the data and wrote the article. Yuichi Adachi and Akira Akasawa designed the study protocol and cowrote the article. Masayuki Akashi, Yukihiro Ohya and Hiroshi Odajima designed the study protocol. Toshiko Itazawa and Yoko Murakami analysed the data and discussed the results.

Conflict of interest

All authors declare that there are no conflicts of interest.

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In summary, in this large, nationally representative sample of more than 600 asthmatic patients, we found that triclosan exposure was associated with a more than 70% increased risk of reporting an asthma exacerbation in the last year. Exposure to triclosan may directly lead to asthma exacerbations, or elevated triclosan levels may be a marker for poor asthma control. Future prospective studies are needed to determine whether triclosan exposure has a role in the development and maintenance of allergy and allergic respiratory disease.

Supplementary Data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.anai.2013.11.017.

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Test-retest reliability of the International Study of Asthma and Allergies in Childhood questionnaire for a web-based survey

Epidemiologic surveys are essential for providing fundamental insight into allergic diseases. However, in epidemiologic studies that use traditional approaches, such as paper questionnaires and interviews, the response rates have decreased in the past decades. This issue was even raised by the International Study of Asthma and Allergies in Childhood (ISAAC).[1] The median response rates of active consents in the 6- to 7-year age group decreased from 84% in phase 1 to 78% in phase 3, which was conducted 7 years after phase 1.[2] Another approach to data collection using the Internet is increasing in academic research.[3] However, web-based surveys accounted for only 1% of epidemiologic articles in the 7 high-impact general medical and epidemiologic journals from 2008 to 2009.[3] One of the reasons for this finding might be that there are few studies that investigate the reliability of the data collected via the Internet. Thus, this study aims to evaluate the reliability of the web-based ISAAC questionnaire.

This study was conducted using the Macromill online research system (Macromill Inc, Tokyo, Japan), which maintains one of the largest research panels in Japan. Among the 2,598 monitors who resided in the Kyushu region and had children aged 6 to 12 years based on their background data, we randomly selected 958 parents to participate in the survey in September 2011 (time 1 survey). If a parent had 2 or more children aged 6 to 12 years, they were asked to complete the questionnaire for each child, and 1,254 children were recruited. For the test-retest study, we randomly selected 200 children from the children who participated in the time 1 survey and asked their parents to complete the same questionnaire in October 2011 (retest survey).

We used the web-based ISAAC questionnaire based on the Japanese version of the written questionnaire. It was a multiple-page design and automatically skipped questions that were irrelevant to the respondent. We estimated the prevalence of allergic symptoms based on the responses to the ISAAC core questions.[1] Demographic differences among the study participants were compared using the χ^2 test or the Mann-Whitney test. $P < .05$ was considered statistically significant. Reliability was assessed using the proportion of agreement and the κ coefficient. All analyses were performed using SPSS statistical software, version 19 (IBM, Armonk, New York). The study protocol was approved by the independent review board of the Tokyo Metropolitan Children's Medical Center.

A total of 184 study participants (93 boys and 91 girls; mean [SD] age, 8.8 [1.8] years) were analyzed for the assessment of test-retest reliability. The respondent characteristics between the time 1 survey and the retest survey were not significantly different. Life-long prevalence of allergic symptoms, especially skin symptoms, tended to be higher than the current prevalence (Table 1). The proportion of agreement for the questions on asthma and nose and/or eye symptoms was more than 90%, whereas that for the questions on eczema was less than 90%. The questions on current symptoms had κ coefficients between 0.55 and 0.64. Of interest was that the κ coefficients for the question on current eczema was lower than that for the question on eczema ever, which was opposite of those for respiratory symptoms.

This study found that the web-based ISAAC questionnaire was reliable for the epidemiologic survey. Population-based studies using

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Table 1
Prevalence of allergic symptoms, proportion of agreement, and κ coefficients

Variable	Prevalence, %		Proportion of Agreement, %	κ Coefficient (95% Confidence Interval)
	Time 1	Retest		
Current wheeze	12.5	14.7	91.3	0.63 (0.46-0.80)
Asthma ever	18.5	19.0	94.0	0.80 (0.69-0.92)
Current allergic rhinoconjunctivitis	13.6	14.7	91.3	0.64 (0.48-0.80)
Pollinosis ever	15.2	14.1	94.6	0.78 (0.65-0.91)
Current eczema	13.0	13.6	89.7	0.55 (0.37-0.73)
Eczema ever	39.7	41.8	75.0	0.48 (0.35-0.61)

the ISAAC written questionnaire have produced similar κ coefficients to our results. A test-retest study of the ISAAC written questionnaire conducted in Malaysian children aged 7 to 12 years after a 1-month interval demonstrated that the κ coefficients for the questions on asthma, rhinitis, and eczema were 0.63 to 0.81, 0.49 to 0.52, and 0.34 to 0.83, respectively.[4] In an Italian study performed 3 months apart in adolescents, the ISAAC written questionnaire revealed κ coefficients between 0.41 and 0.86 for the questions on asthma.[5] Furthermore, a randomized study that compared web-based and written ISAAC questionnaires on respiratory symptoms found that both questionnaires yielded equal results in adolescents.[6]

For the questions regarding respiratory or nose and/or eye symptoms, the questions using "ever" as a reference period tended to have higher reliability than those using "in the past 12 months." Similar results were found in the Malaysian and Italian studies.[4,5] In contrast, the reliability of the question on eczema ever tended to be lower than that on current eczema. The prevalence of current eczema was one-third of that of eczema ever, which means that many children diagnosed as having eczema in infancy outgrow it when they reach school age. Although recalling symptoms experienced during a lifetime might be easier than recalling symptoms during specific intervals, recalling the symptoms only seen in infancy might be less likely to be reliable in a study conducted in schoolchildren. Compared with higher reliability of the questions on respiratory and nose and/or eye symptoms, reliability of the questions on eczema was lower, consistent with the results of the Malaysian study.[4] This lower reliability might be explained by languages and cultural backgrounds. The ISAAC phase 3 study group reported that some English terms were difficult to translate into other languages despite a detailed protocol.[7] Terms such as *itchy rash* and *eczema* might have their own interpretation problems in Japanese along with Bahasa Malaysia.[4] Although the Japanese version of the ISAAC questionnaire used footnotes to describe skin lesions, our results suggested that the language problems persisted.

The limitation of this study was the concern about generalizability; people who did not have access to computers with Internet connections could not participate in this study. The Ministry of Internal Affairs and Communications in Japan (http://www.soumu.go.jp/johotsusintokei/english/) revealed that the Internet diffusion rate among people aged 20 to 49 years exceeded 90%, which means that most parents of schoolchildren currently use the Internet in Japan.

The web-based ISAAC questionnaire was found to be as reliable as the written one and could become a new research tool when the target population has a high Internet penetration rate. Further studies are needed to create a web-based questionnaire using multimedia, such as sound and visual content, which would lead to further improvement in the reliability of questionnaires.

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Urinary biopyrrin: a potential inflammatory marker of atopic dermatitis

Atopic dermatitis (AD) is a chronic and relapsing eczematous disease that is generally associated with allergen-induced skin inflammation. Chronic persistent inflammation by free radicals is postulated to impair skin barrier function, leading to dry skin and sustained pruritus; therefore, excessive oxidative stress is postulated to exacerbate the inflammatory process of AD.[1] In children with AD, levels of urinary 8-hydroxydeoxyguanosine, a product of nucleic acid oxidation, are indeed elevated according to disease severity.[2]

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Present state of Japanese cedar pollinosis: The national affliction

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Seasonal allergic rhinitis (SAR) caused by Japanese cedar pollen (JCP; ie, sugi-pollinosis) is the most common disease in Japan and has been considered a national affliction. More than one third of all Japanese persons have sugi-pollinosis, and this number has significantly increased in the last 2 decades. In our opinion the reason why sugi-pollinosis became a common disease in the last half century is the increased number of cedar pollens, with global climate change and forest growth caused by the tree-planting program of the Japanese government after World War II playing substantial roles; dust storms containing small particulate matter from China might also contribute to the increased incidence of sugi-pollinosis. To help minimize their symptoms, many Japanese wear facemasks and eyeglasses at all times between February and April to prevent exposure to JCP and aerosol pollutants. Forecasts for JCP levels typically follow the weather forecast in mass media broadcasts, and real-time information regarding JCP levels is also available on the Internet. Because a large amount of JCP is produced over several months, it can induce severe symptoms. Japanese guidelines for allergic rhinitis recommend prophylactic treatment with antihistamines or antileukotrienes before the start of JCP dispersion. Additionally, sublingual immunotherapy will be supported by health insurance in the summer of 2014. However, many patients with sugi-pollinosis do not find satisfactory symptom relief with currently available therapies. Collaboration between scientists and pharmaceutical companies to produce new therapeutics for the control of sugi-pollinosis symptoms is necessary. (J Allergy Clin Immunol 2014;133:632-9.)

Key words: *Seasonal allergic rhinitis, Japanese cedar, global climate change, prophylactic treatment, alternative complementary treatments*

Allergic rhinitis (AR) represents a global health care problem that greatly affects daily activity, work productivity, learning, sleep, and quality of life (QOL) in persons of all ages. In the Allergic Rhinitis and its Impact on Asthma study, AR is divided into 2 categories: intermittent or persistent disease.[1] However, many otorhinolaryngologists in Japan use a perennial allergic rhinitis (PAR) and seasonal allergic rhinitis (SAR) classification system.[2] The major allergen contributing to SAR in Japan is pollen from the Japanese cedar (*Cryptomeria japonica*; ie, sugi). SAR is caused by Japanese cedar pollen (JCP; ie, sugi-pollinosis) and was first reported in 1963.[3] During the height of the allergy season (between February and April), a large number of patients with sugi-pollinosis experience more severe symptoms for longer periods of time compared with other pollen allergies (Fig 1, *A*). This might be because JCP is dispersed in large quantities over long distances (>100 km in some cases) and can remain airborne for more than 12 hours (Fig 1, *B*).[4] Furthermore, pollen from the Japanese cypress *(Chamaecyparis obtusa)*, which also causes SAR, is dispersed in April and May, immediately after the release of JCP. Because Japanese cypress pollens are considered to contain several components that cross-react with JCP, 70% of patients with sugi-pollinosis also experience SAR caused by Japanese cypress pollen. Therefore allergic symptoms can last for as long as 4 months, from February to May, with some variation caused by annual climate differences.

A meta-analysis of 38 reports representing 27 prevalence subgroups and 134 sensitization rate subgroups showed that the prevalence of sugi-pollinosis increased 2.6-fold between 1980 and 2000.[5] The prevalence of sugi-pollinosis was 19.4% of the Japanese population in 2001.[6] We conducted a survey of 1540 persons aged 20 to 49 years in Fukui City between 2006 and 2007 that indicated the positive rate of serum JCP-specific IgE was 56.3% and the prevalence of sugi-pollinosis was 36.7%.[7] Additionally, the International Study of Asthma and Allergies in Childhood showed that Tokyo schoolchildren have an extremely high prevalence of SAR.[8,9] Specific to Japan, SAR-JCP is now called a national affliction. Manufacturers and

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Abbreviations used

AD:	Asian dust
apoA-IV:	Apolipoprotein A-IV
AR:	Allergic rhinitis
GWAS:	Genome-wide association study
JCP:	Japanese cedar pollen
PAR:	Perennial allergic rhinitis
PM:	Particulate matter
PM2.5:	Particulate matter less than 2.5 μm in diameter
QOL:	Quality of life
SAR:	Seasonal allergic rhinitis
SLIT:	Sublingual immunotherapy
Sugi-pollinosis:	Seasonal allergic rhinitis caused by Japanese cedar

retailers are set to tap into a soaring demand for medications and related items, and the market for JCP prescription drugs has soared to 200 to 300 billion yen per season (2.1-3.2 billion US dollars). Also, the government will be required to take effective actions.

In this review we introduce sugi-pollinosis, the national affliction of Japan, with the intention of informing allergists about the spectrum of symptoms and treatment options available for patients with sugi-pollinosis.

PUTATIVE TRIGGER FACTORS, ENVIRONMENT, AND PATHOLOGY FOR THE INCREASED PREVALENCE OF SUGI-POLLINOSIS

In Japan forests cover approximately 25 million hectares (ie, 66% of the total area of Japan). More than half of these trees were planted from the early 1950s to the early 1970s, and according to the Forestry Agency of Japan, an estimated 4.6 billion of these are Japanese cedar trees, covering nearly 18% of the total land area of Japan. The sugi trees are extremely straight and tall, making them ideal construction materials, but after wood tariffs decreased in 1964, imported wood put the sugi foresters out of business, and most sugi trees have been abandoned and grow taller and produce more pollen each year. With the exception of Hokkaido and Okinawa islands, this yellow-green dust is scattered throughout Japan. Airborne JCP levels have been monitored in Sagamihara hospital (Kanagawa, Japan) since 1965. JCP counts can vary significantly from year to year because of weather conditions; however, the total JCP counts from 1995 to 2013 have been significantly greater than those in the initial period from 1965 to 1994 ($P < .05$; Fig 2, *A*).

Epidemiologic studies have demonstrated that global climate change correlates with the number of symptomatic pollen-induced respiratory allergies and allergic diseases.[10,11] One of the fundamental effects of climate change is the potential for shifts in flowering phenology and pollen production associated with warmer seasonal air temperatures. As such, the length of the sugi-pollinosis season has increased since 1995.[12] Although the average global temperature has only increased by approximately 0.6°C in the 20th century, climate change in Japan has been more severe, with temperatures increasing by an average of 1.15°C in the past 100 years. Fig 2, *B*, shows the annual temperature change since 1960 in Japan.

Cedar pollen is released from male flowers on sugi trees (Fig 1, *C*). Hot summers usually affect sugi trees, promoting flower bud development and increasing pollen production; meanwhile, cool summers have opposite effects. Ito et al[13] investigated the correlation between total JCP count and the previous years' summer weather conditions from 1987 to 2006. The annual cumulative level of airborne JCP was significantly related to the mean temperature and sunlight hours in late July before the start of the pollen season (see Table E1 in this article's Online Repository at www.jacionline.org). The mean temperature in July during the 20th century has also significantly increased in Japan. Average temperatures in the Fukui area from 1974 to 1993 and 1994 to 2012 were 25.1°C ± 0.3°C and 26.2°C ± 0.3°C, respectively ($P < .05$; Fig 2, *C*). The weather of late winter and early spring was not correlated with JCP counts; however, temperatures in January and February did influence the start of sugi pollen production and the pollen season (data not shown).

JCP counts were significantly associated with the prevalence of sugi-pollinosis. The mean JCP count in the mountainous area of Akita prefecture was 2 times higher than that in the coastal area of Akita from 1996 to 2006 (see Table E2 in this article's Online Repository at www.jacionline.org). The prevalence of sugi-pollinosis in children (age, 10-11 years) in 2006 was higher in mountainous areas than in coastal areas, although the prevalence of PAR was not different between the 2 areas (see Table E3 in this article's Online Repository at www.jacionline.org). The positive rate of serum anti-JCP–specific IgE in the mountainous area was also higher than in that in the coastal areas, but the positive rate of anti-mite IgE did not increase in the mountainous area.[14]

Asian dust (AD) and urban particulate matter (PM) are risk factors for sugi-pollinosis. AD storms originating in the deserts of Mongolia, northern China, and Kazakhstan are seasonal phenomena that affect much of Eastern Asia, including Japan, and occasionally spread around the globe, affecting the United States as well.[15] The number of spring dust storms has increased in the last 13 years. The frequency of the storms combined with increases in airborne pollution has led to an increase in the adverse effects of the storms. AD contains pollutants, such as sulfur dioxide and nitrogen dioxide, which stimulate immune cells through oxidative stress, enhancing inflammation-related cytokines.[16] AD enhanced nasal allergic reactions induced by repeated JCP administration in guinea pigs.[17] In fact, allergic symptoms have increased during AD storm events in Japan and Taipei.[18,19] Administration of AD plus allergen induced allergen-specific IgE production in mice,[20] suggesting that AD can bind to JCP and induce JCP sensitization in nonatopic or unsensitized atopic subjects.

The main pollutant in Japanese cities is fine PM. Particulate matter less than 2.5 μm in diameter (PM2.5) is frequently reported in spring. PM2.5, a component of AD, induced asthma and enhanced sneezing and rhinorrhea in a manner of type I allergy.[21] Beijing has also recorded its worst levels of air pollution in recent years, and the onset and sensitization of sugi-pollinosis could be easily induced by PM2.5 from China. Environmental authorities in Japan, the United States, and other nations have adopted strict regulations to control PM levels. A wave of criticism, both at home and abroad, prompted Chinese officials to set their own standards in February 2012; however, air quality in China still remains an issue.

GENETIC FACTORS

Genome-wide association studies (GWASs) and meta-analyses of GWASs have shown both common and distinct pathways that

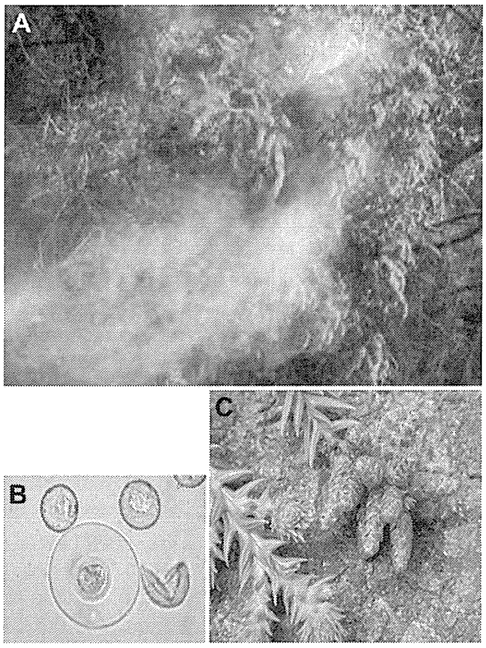

FIG 1. The blooming Japanese cedar tree. **A,** Yellow-green pollen is scattered from male Japanese cedar flowers. **B,** JCP (magnification ×400). **C,** Male *(right)* and female *(left)* flowers of Japanese cedar.

might contribute to asthma and allergic diseases.[22,23] The first GWAS of asthma identified a novel asthma susceptibility locus on chromosome 17q21 including the *ORMDL3* genes.[24] Five polymorphisms in the *ORMDL3* gene are significantly associated with sugi-pollinosis.[25] Additionally, the matrix metalloproteinase 9 gene is involved in the pathogenesis of AR and asthma. The matrix metalloproteinase 9 gene confers susceptibility to sugi-pollinosis in children and might be associated with sensitization processes.[26] One of the polymorphisms in the gene for the IL-4 receptor α chain, the Ile50 allele, might be involved in both sugi-pollinosis and atopic dermatitis.[27] IL-33 (an IL-1–like cytokine) is a ligand for IL-1RL1, an important effector molecule of the T_H2 response. Serum levels of IL-33 are significantly higher in patients with sugi-pollinosis than in their nonallergic counterparts. In a genetic association analysis we found a positive association between the polymorphism of IL-33 and sugi-pollinosis.[28]

Complement systems are known to play an important role in allergic diseases. Decay-accelerating factor, which is involved in the regulation of the complement system, is one of the genes involved in conferring susceptibility to AR and sugi-pollinosis. Low levels of decay-accelerating factor might be associated with the enhanced specific IgE response that occurs in patients with allergic diseases in the Japanese population.[29]

Microarray analysis showed that JCP exposure increased IL-17 receptor β RNA expression in patients with sugi-pollinosis.[30]

ASSESSMENT OF SEVERITY

Nasal symptom scores are assessed with a grading system that includes sneezing, rhinorrhea, and nasal congestion in Japan. Symptom scores are graded from 0 to 4. Grading of sneezing, rhinorrhea, and nasal congestion are evaluated based on the frequency of sneezing (number per day), frequency of nasal blowing (number per day), and duration of mouth breathing, respectively (Fig 3).[31] Total nasal severity of sugi-pollinosis is evaluated by using the grading scores of nasal obstruction and sneezing/rhinorrhea as very severe, severe, moderate, and mild symptoms. According to Fig 3, of 795 patients with sugi-pollinosis, 22.6%, 29.4%, 31.3%, and 13.9% had very severe, severe, moderate, and mild symptoms, respectively.[32] Ninety-one percent of patients with sugi-pollinosis are classified as having moderate-to-severe AR.[32]

ENVIRONMENTAL EXPOSURE UNITS

There are 4 environmental exposure units in Chiba, Tokyo, Wakayama, and Osaka City to investigate the effectiveness of medicine or devices on sugi-pollinosis (Fig 4).[33]

ELIMINATION AND AVOIDANCE OF ANTIGENS

The most effective means of decreasing allergic inflammation reactions is avoidance of the aeroallergen.[1] Although the complete avoidance of pollen is impossible because of its ubiquitous nature, patients with sugi-pollinosis often wear protective facemasks between February and May (Fig 5); these masks have a significant protective effect on nasal JCP invasion.[34] This has created a large market for an array of related devices. Forecasting daily JCP dispersal conditions can help patients decide which prevention measures to take to protect them from pollen inhalation (see Fig E1 in this article's Online Repository at www.jacionline.org). Using a service unique to Japan that has not been adopted in other countries, the amount of airborne JCP is automatically counted with equipment set up on the roofs of 1000 buildings and connected to the Internet (see Fig E2 in this article's Online Repository at www.jacionline.org). The information is gathered from these sites and can be accessed for free using the Internet service. Furthermore, the success of these automatic pollen counters has led to their use to assess levels of other pollens, such as Urticaceae, Poaceae, and *Ambrosia* species.[35]

Ventilation systems can be equipped with appropriate filters to avoid drawing JCP into the house and car. Novel air-purification systems using positively and negatively charged cluster ions have been developed to create comfortable indoor living environments. Treatment with positive and negative cluster ions significantly decreased the *in vitro* and *in vivo* antigenicity of atomized JCP.[36] Treatment with low-concentration hypochlorous acid generated by means of electrolysis is also an effective method for significantly reducing the immunogenicity of JCP.[37]

PHARMACOTHERAPY

Therapy for sugi-pollinosis is chosen based on severity (Fig 3) and disease type (Fig 6).[2,38] Because the severity of pollinosis markedly changes with the amount of dispersed pollen, the severity of a patient's symptoms is determined during a medication evaluation at peak pollen dispersal times and also takes into account the amount of dispersed pollen. Nasal antihistamine and mast cell stabilizers were not used for 1 decade in Japan.

Because there are a large number of patients with severe or very severe sugi-pollinosis, Japanese guidelines recommend the prophylactic treatment of sugi-pollinosis before pollen release.[2] Prophylactic treatment with oral antihistamines (olopatadine) significantly suppressed nasal symptoms by 40% and was

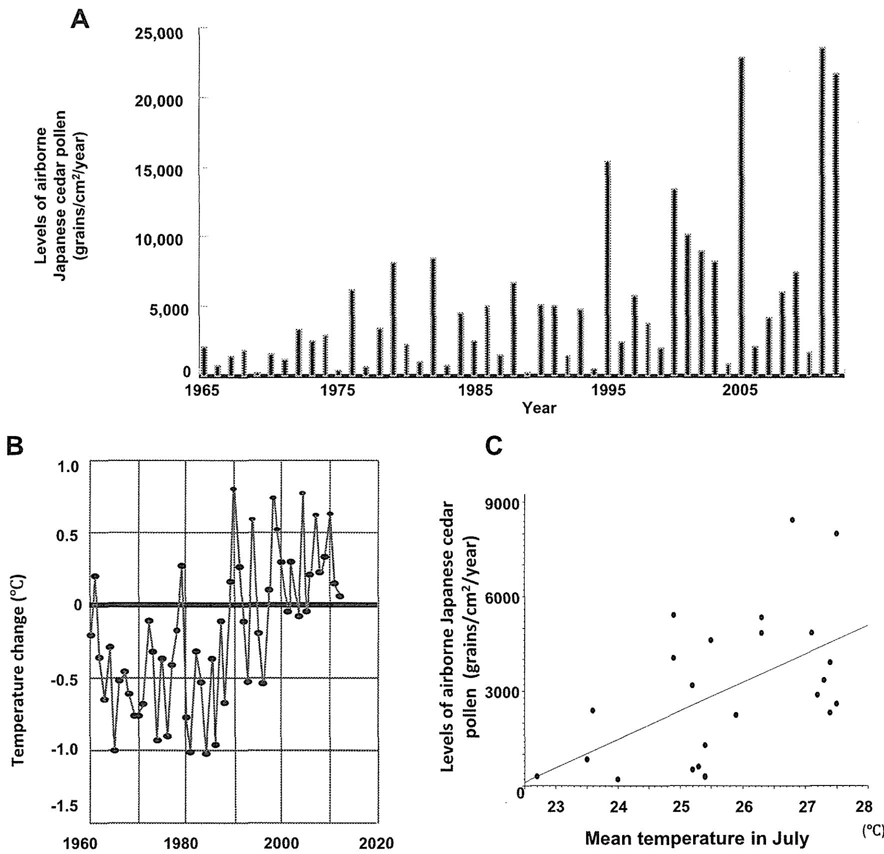

FIG 2. Correlation between increased JCP counts and climate change. **A,** Annual JCP counts from 1965 to 2013 in Kanagawa prefecture. **B,** Annual temperature change in Japan compared with baseline (mean temperature from 1960 to 2012). Data were provided by the Japan Meteorological Agency. **C,** Correlation between annual cumulative levels of airborne JCP and the mean temperature in Fukui, Japan. The mean temperature was taken in late July before the pollen season and from 1988 to 2012 (Spearman rank correlation coefficient = 0.531, *P* = .0067). Pollen counts were determined from daily data with the Durham sampler (the standard gravity slide sampler) by counting the JCP particles dropped onto glass microscope slides.

associated with a high level of QOL during the peak of the JCP season in a randomized, double-blind, placebo-controlled study.[39]

Prophylactic administration of antileukotriene (pranlukast) 1 to 2 weeks before or at the start of the JCP season significantly reduced nasal symptoms by 50% at the peak of pollen dispersal compared with placebo.[40] Additionally, antileukotrienes reduces nasal congestion and allergic inflammation in patients with sugi-pollinosis.

Intranasal corticosteroids are the most effective drugs for controlling AR. In a double-blind, randomized, placebo-controlled study with mometasone furoate nasal spray (MFNS) as a prophylactic treatment for sugi-pollinosis, no worsening occurred in the MFNS group, whereas the placebo group showed a significant worsening of symptoms after the start of the continuous dispersion.[41] The 12-week mean total nasal symptom score in the prophylactically treated group was significantly lower than that in the postonset-treated group (which reduced the symptoms by 61%).[42] Intranasal corticosteroids should be administered prophylactically; with the addition of an oral antihistamine, they might improve outcomes in patients with severe sugi-pollinosis.[43] However, many Japanese persons prefer not to use intranasal corticosteroids because of personal issues associated with using nasal sprays, including their smell.

IMMUNOTHERAPY

Antigen-specific immunotherapy can change the natural course of AR and is recognized as a curative treatment without impaired performance. In the 1970s, subcutaneous immunotherapy for sugi-pollinosis was performed at university hospitals and medical clinics.[44] However, in the 1980s, the development of second-generation antihistamines and intranasal corticosteroids gradually decreased the frequency of application of subcutaneous immunotherapy. This decrease was also attributable to the fact that JCP extracts were not standardized until 1999.

In 2004, a multicenter, double-blind, randomized, placebo-controlled, parallel-group study of sublingual immunotherapy (SLIT) demonstrated the safer and more beneficial effects of immunotherapy for sugi-pollinosis than pharmacotherapy alone.[45,46] The mean of the daily total symptom scores was significantly lower in the SLIT group than in the placebo group. The QOL score in the SLIT group was almost half that in the placebo group.

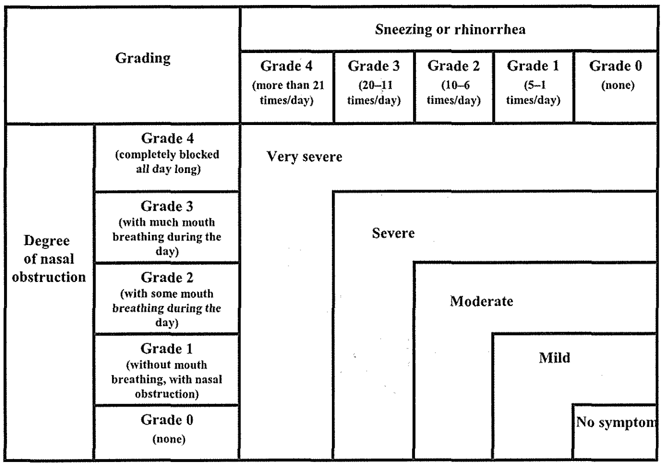

FIG 3. Classification of the total severity of nasal symptoms of AR. Grading of sneezing, rhinorrhea, and nasal obstruction is evaluated based on the frequency of sneezing or the frequency of nasal blowing per day and the duration of mouth breathing. High grading scores are selected from sneezing or rhinorrhea. Uncontrollable severe symptoms are classified as very severe.

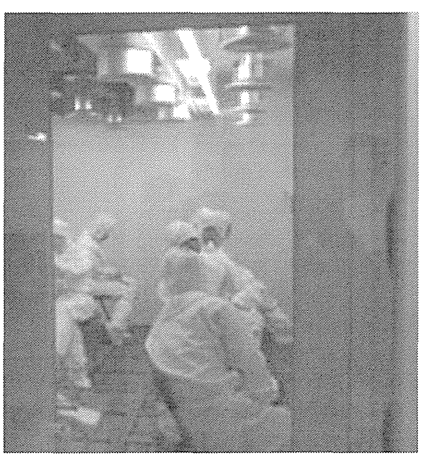

FIG 4. An environmental exposure unit.

Sera from 25 patients with sugi-pollinosis in a double-blind, randomized, placebo-controlled study for SLIT were analyzed by using 2-dimensional electrophoresis.[47] Sixteen proteins were found to be differentially expressed during the pollen season. Among the differentially expressed proteins, serum levels of apolipoprotein A-IV (apoA-IV) were significantly increased in SLIT-treated patients but not in placebo-treated patients. Higher levels of apoA-IV induction were correlated with lower clinical symptom–medication scores and better QOL scores in the case of SLIT-treated patients. The amount of histamine released from basophils *in vitro* was significantly reduced after addition of recombinant apoA-IV in the medium.[47] SLIT increased IL-10 production by monocytes and T cells in patients with sugi-pollinosis.[48] ApoA-IV and IL-10 might become clinical markers for the evaluation of the effectiveness of SLIT for sugi-pollinosis.

Uses of antigen-derived peptides that retain immunogenicity (but are insufficient in length to cross-link IgE on mast cells or basophils [immunotherapeutic peptides]) are a promising strategy for improved immunotherapy, and this concept has been applied to a variety of allergens. Cry-consensus peptide for sugi-pollinosis contains 6 major human derived T-cell epitopes. In an AR mouse model Cry-consensus peptide markedly inhibited Cry j 1–induced sneezing, eosinophil infiltration, and eosinophil peroxidase activity in nasal tissue.[49] Human immunodominant T-cell epitopes of the Cry j 1 molecule are being studied for peptide-based immunotherapy in patients with sugi-pollinosis.[50]

FIG 5. Persons on a train platform in a large Japanese city wearing facemasks during the JCP season.

ANTIBODY THERAPY

Omalizumab, a recombinant, humanized, anti-IgE mAb, has been shown to be effective for the treatment of SAR.[51] A randomized, placebo-controlled, double-blind study was conducted in Japanese patients with a history of moderate-to-severe sugi-pollinosis. The primary and all secondary efficacy variable scores were significantly lower in the omalizumab group than in the placebo group.[52] Retreatment with omalizumab is effective and safe when readministered in the second JCP season.[53]

PROBIOTICS

Probiotics, including lactobacilli and bifidobacteria, might prevent several allergic diseases. Japanese persons are very interested in probiotics for the self-treatment of AR. A double-blind, placebo-controlled trial with lyophilized powders of *Bifidobacterium longum* BB536 for the treatment of sugi-pollinosis during the height of the pollen season indicated that BB536 intake alleviated subjective symptoms, reduced prescription of allergic medicines, and significantly suppressed the increase of plasma thymus and activation-regulated chemokine during the pollen season.[54] In another study BB536 reduced nasal symptoms from early allergic reactions in patients with sugi-pollinosis exposed to JCP in an environmental exposure unit outside of the normal JCP season.[55] Oral administration of heat-killed *Lactobacillus gasseri* OLL2809 reduced nasal

Severity	(prophylactic treatment)	Mild	Moderate		Severe or very severe	
Types			Sneezing rhinorrhea	Nasal blockage or combined	Sneezing rhinorrhea	Nasal blockage type or combined
Choice of therapy	Oral histamine H_1 antagonists (2nd generation) or Oral Th2 cytokine inhibitors or Oral leukotriene receptor antagonists or Oral Prostaglandin D2/ Thromboxane A2 receptor antagonists	Oral histamine H_1 antagonists (2nd generation) + Eye drops, + Intranasal corticosteroid (when needed)	Oral histamine H_1 antagonists (2nd generation) + Intranasal corticosteroid	Oral leukotriene receptor antagonists + Oral histamine H_1 antagonists (2nd generation) + Intranasal corticosteroid	Intranasal corticosteroid + Oral histamine H_1 antagonists (2nd generation)	Intranasal corticosteroid + Oral leukotriene receptor antagonists + Oral histamine H_1 antagonists (2nd generation)
						+ Intranasal vasoconstrictor nose spray 7 to 10 days + oral corticosteroid 4-7 days (when needed, at the start of treatment)
		Histamine H_1 eye drops antagonists or mast cell stabilizer			Histamine H_1 eye drops antagonists, mast cell stabilizer, or steroids	
					Operation for cases of nasal blockage type with nasal deformities.	
	Specific immunotherapy					
	Avoidance and elimination of antigens					

FIG 6. Algorithm for the treatment of sugi-pollinosis recommended by Japanese guidelines.[2]

symptoms and JCP-specific IgE levels.[56] Additionally, oral administration of *Lactobacillus paracasei* strain KW3110 decreased total symptom scores and serum eosinophil cationic protein levels and improved QOL scores at the start of the JCP production season.[57]

In addition, dietary intervention with nondigestible prebiotics might be effective for allergic diseases.[58] Administration of β-1, 4 mannobiose decreased sneezing frequency, histamine release, and IL-4 production in a sugi-pollinosis mouse model, suggesting a potential molecular therapeutic supplement in clinical trials for sugi-pollinosis.[59,60]

FLAVONOIDS AND TEA

An appropriate intake of flavonoids might constitute a dietary preventative or therapeutic strategy for allergic diseases because flavonoids, which are abundant in plant foods, possess antioxidants and antiallergic activities. Analyses of structure-activity relationships of 45 flavones, flavonols, and their related compounds showed that luteolin, ayanin, apigenin, and fisetin were the strongest inhibitors of IL-4 production by basophils in mice because of their inhibitory action on the activation of nuclear factors in activated T cells and activator protein 1.[61] Additionally, prophylactic ingestion of enzymatically modified isoquercitrin significantly decreased levels of ocular symptoms and medication scores in patients with sugi-pollinosis in a double-blind, placebo-controlled study.[62]

Self-care with Ten-Cha (*Rubus suavissimus*, sweet Chinese tea) is the most common alternative complementary treatment for AR in Japan. Ten-Cha extract inhibited histamine release from rat peritoneal mast cells, as well as calcium ionophore–induced vascular permeability. However, the effects of drinking Ten-Cha beverages on sugi-pollinosis symptoms were considered low in an unblinded study.[63] Nevertheless, Ten-Cha has sold very well during JCP seasons.

CONCLUSION

In Japan, 69.7% of the adult population has positive results for one of 7 aeroallergen-specific IgEs (JCP, 2 types of mite, ragweed, orchard grass, and *Aspergillum* and *Candida* species), and the prevalence of patients with AR is 44.2%.[7] In response to the increasing demand for AR relief, second-generation antihistamines have been approved for sale as over-the-counter medications. However, present therapies still do not offer sufficient relief for patients with sugi-pollinosis. In addition, the Japanese government has reduced the budget for AR research because they consider more lethal diseases, such as cancer, to be a more serious threat than sugi-pollinosis. Therefore cooperation between scientists and pharmaceutical companies will be needed to find new treatments that better control AR and its symptoms.

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