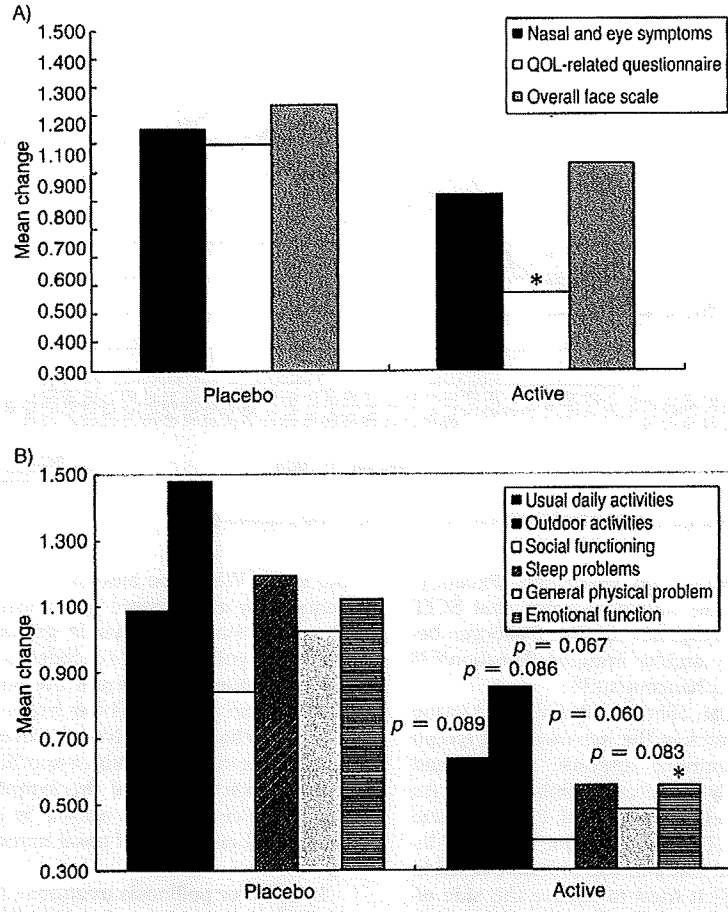

Fig. 3 The mean change of QOL score. A), total QOL scores; B), health related QOL fields.

immunotherapy requiring a new route of administration, such as local immunotherapy, and treatment that does not cause anaphylaxis, such as peptide therapy.[31]

In the comparison of double blinds RCT of the immunotherapy by a SLIT and the SCIT examination, the report is still few.[32] As for the level of the side effect frequency and the effect, it is uncertain. The score of the symptom medicine passes low through the pollen dispersion all seasons. This shows that the drug use decreases in SLIT and corresponding to the result of the RCT examination that uses the placebo.[33] It is thought that the effect equal with the drug use is shown, and a SLIT from which the use of the medicine is decreased is useful in economy. In SLIT studies in Japan, SLIT both inhibited the exacerbation of symptoms in the latter half of the season and reduced their severity throughout the season. Furthermore, there were neither local nor systemic side effects, as reported elsewhere for other antigens.

SLIT for cedar pollinosis is a new therapy and in the future SLIT may by indicated for patients with nasal allergy caused by other allergens such as house dust mites or animal dander through improvement of the administration schedule and establishing the dose at which the most potent effects are achieved.

It is the Ministry of Health, Labour and Welfare science research expense subsidy immunity and an allergy prevention treatment research grant (H14-immunity-001), (H17-immunity-general-001), as for development in this SLIT Japan. It is now progressing as a multicenter study in "Research of the ideal way of information on the real-time monitor pollen count and clinical research on sublingual peptide and the adjuvant therapy (H20-immunity-general-003)".

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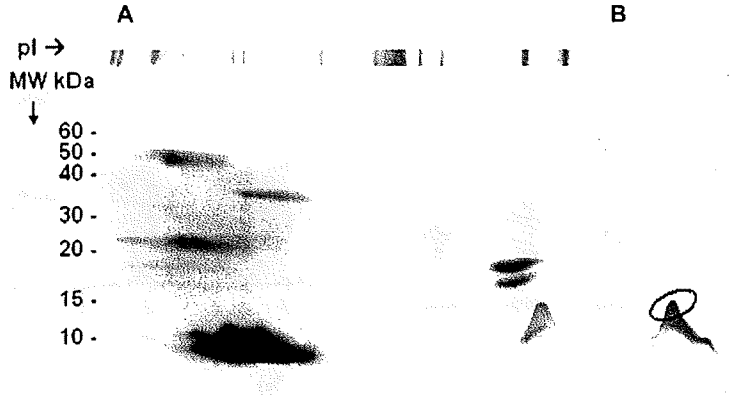

FIG 2. Two-dimensional electrophoresis/immunoblotting of pitaya fruit extract: first dimension, pH 3 to 10; second dimension, 15% SDS-PAGE. A, Protein staining (Coomassie blue) of the 2-dimensional electrophoresis. B, Immunoblot depicting the IgE reactivity of the patient's serum. The *marked spot* was excised and N-terminally sequenced.

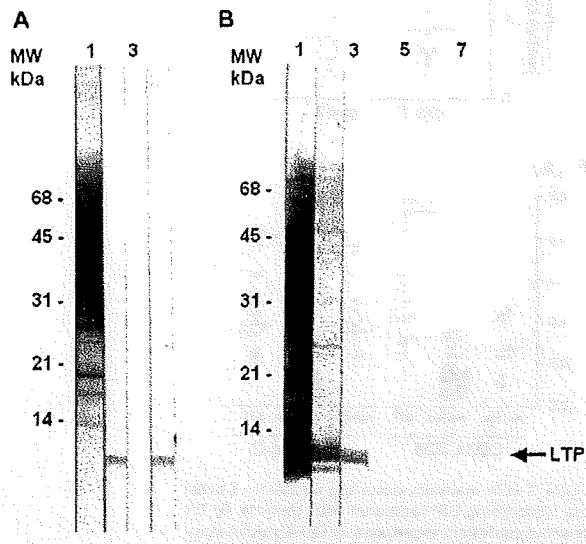

FIG 3. Western blot inhibition test. A, Western blot of pitaya fruit extract under nonreducing conditions, 15% SDS-PAGE: inhibition experiment. *1*, protein staining (India Ink); *2–4*, IgE reactivity of the patient's serum without inhibitor *(2)*, with pitaya fruit extract as inhibitor *(3)*, and with rTri a 14 (wheat LTP) as inhibitor *(4)*. B, Western blot of peach extract containing Pru p 3 (LTP) under nonreducing conditions, 15% SDS-PAGE: *1*, protein staining (India Ink); *2*, rabbit anti–Cor a 8–reactive serum (cross-reacting with Pru p 3); *3* and *4*, Pru p 3–positive sera; *5*, serum of the pitaya-reactive patient; *6*, anti–Cor a 8 control; *7*, anti-IgE control.

This is the second case describing pitaya as an allergenic source eliciting strong allergic reactions. To our knowledge, this is the first time that pitaya nsLTP has been described as an IgE-reactive antigen with the power to elicit anaphylactic responses. The LTPs are a large group of allergens found in many pollen species and fruits.[4] Because this is the second report on an anaphylactic reaction to pitaya in a short time period, this might indicate a higher incidence of sensitization to pitaya and the potential emergence of a wave of new cases of dragon fruit allergy.

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Induction of IL-10–producing regulatory T cells with TCR diversity by epitope-specific immunotherapy in pollinosis

To the Editor:

Specific peptide-based allergen immunotherapy is currently being used for several allergic diseases. Immunotherapy for Japanese cedar pollinosis was undertaken using sublingual application of a pool of pollen peptides containing 7 T-cell epitopes from Cry j 1 and Cry j 2, which are the major Japanese cedar pollen allergens, and its clinical efficacy on seasonal allergic rhinitis was evaluated.[1] Interestingly, some patients undergoing immunotherapy showed reduced sensitivity to other allergens in addition to Japanese cedar pollen. Allergen-specific regulatory T cells have

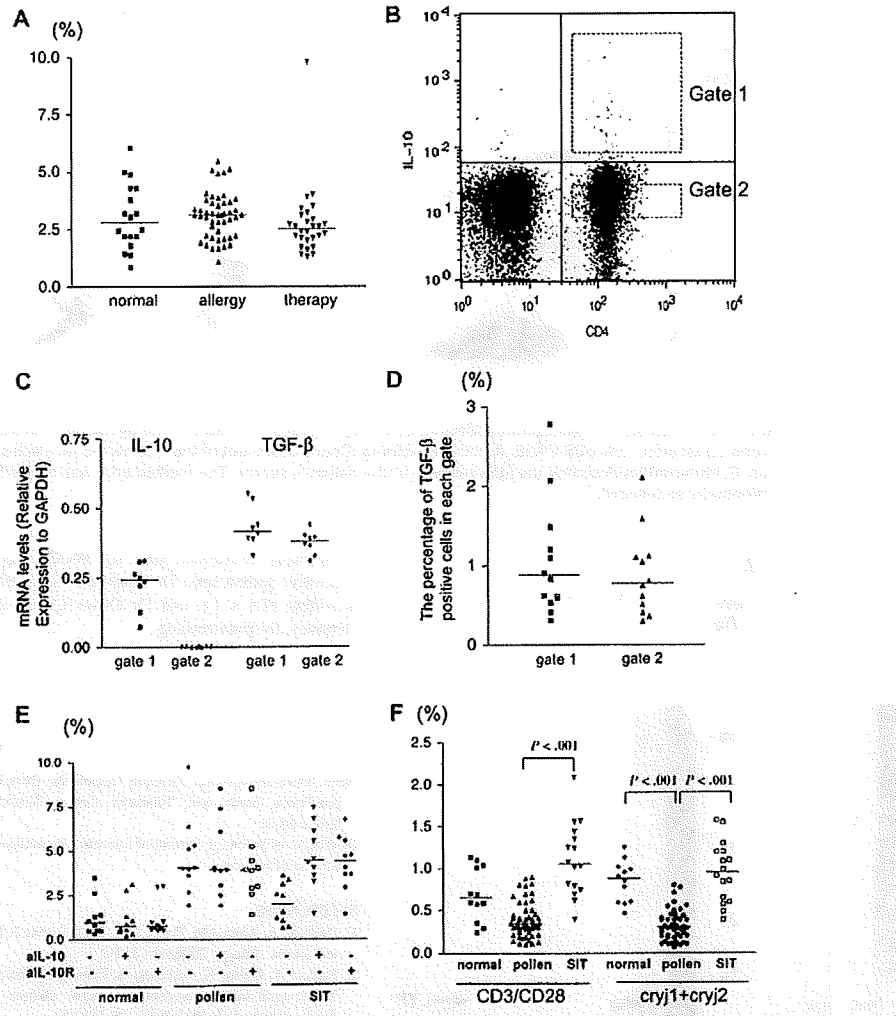

FIG 1. A, The percentage of forkhead box P3$^+$CD25^{high}CD4$^+$ T-cells (naturally occurring regulatory T cells) was unchanged in patients with pollinosis and in those undergoing SIT compared with controls. B, Tr1 *(gate 1)* and non-Tr1 *(gate 2)* cells are gated. C, Tr1 cells show equivalent expression of TGF-β mRNA compared to non-Tr1 cells, different from that of IL-10. D, When cells were costained with anti–TGF-β antibody, the percentage of TGF-β–positive cells was similar between Tr1 *(gate 1)* and non-Tr1 *(gate 2)*. E, CD4$^+$ lymphocyte proliferation was significantly suppressed in PBMCs from patients who received SIT compared with patients with pollinosis. This suppressive function was abolished by the addition of anti–IL-10 neutralizing antibody or anti–IL-10 receptor antibody. F, The percentage of Tr1 cells was significantly decreased in patients with untreated pollinosis compared with normal controls and increased in patients receiving SIT.

been suggested to play a role in this immunoprotection,[2-5] but the precise mechanism is not fully understood.

IL-10–producing regulatory T cell (Tr1) is one type of acquired regulatory T cells with unclear characteristic phenotypes. In the current study, the Tr1 population percentage was compared among untreated patients with pollen allergy, patients undergoing immunotherapy, and healthy subjects. The results showed that the number of Tr1 cells was significantly increased in patients receiving immunotherapy compared with the other groups. In addition, the diversity of the T-cell receptor repertoire in the Tr1 population from patients undergoing immunotherapy was investigated.

Seventy-five patients from the Departments of Dermatology and Otorhinolaryngology of Mie University Hospital were enrolled (15 patients with pollen allergy receiving sublingual immunotherapy [SIT] as described, and 60 sensitive to Japanese cedar). Thirteen healthy controls were also recruited (see details in this article's Table E1 in the Online Repository at www.jacionline.org). Diagnosis was based on clinical symptoms and serological results. Blood was sampled after obtaining written informed consent from all subjects, and the investigational protocol was approved by the Institutional Review Board of Mie University Hospital. Healthy volunteers had no history or subjective symptoms of atopic dermatitis or pollen allergy.

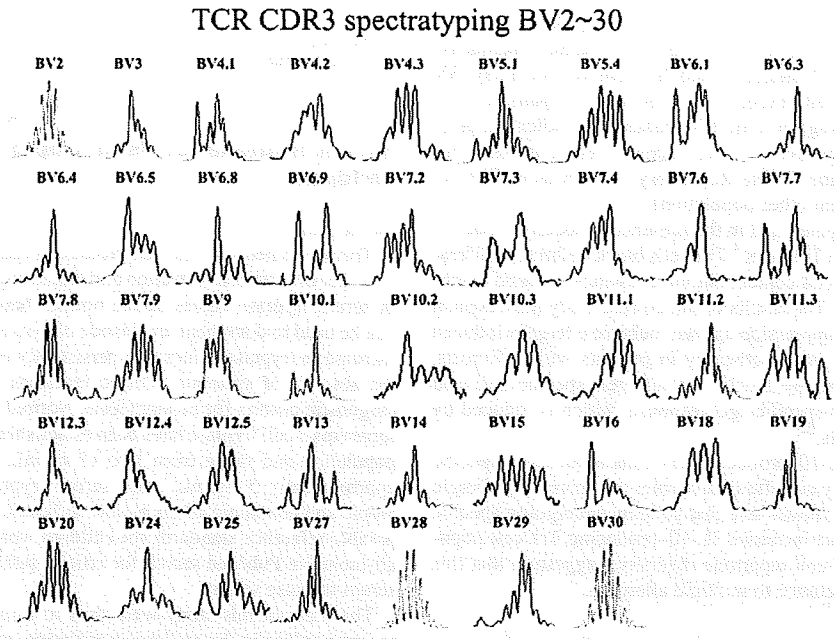

FIG 2. T-cell receptor complementarity-determining region 3 *(CDR3)* size spectratyping analysis of a Tr1 population from patients undergoing immunotherapy. A Gaussian distribution of CDR3 lengths was observed in many BV subfamilies, except for oligoclonal expansion in some BV subfamilies, indicating preservation of a highly diverse T-cell receptor repertoire.

Recent studies have shown a significant decrease of forkhead box $P3^+CD25^{high}CD4^+$T cells, naturally occurring regulatory T cells in symptomatic patients with atopic dermatitis or bronchial asthma.[6] However, the percentage of naturally occurring regulatory T cells (forkhead box $P3^+CD25^{high}CD4^+$T cells/$CD4^+$T cells) remained unchanged in patients with pollinosis and in those receiving SIT compared with controls (Fig 1, *A*). In the current study, the IL-10–producing Tr1 cell population was characterized by flow cytometry and cell sorting. PBMCs from patients and normal donors were isolated from heparinized venous blood by density gradient centrifugation using Ficoll (for antibodies and reagents, see Methods in this article's Online Repository at www.jacionline.org). PBMCs were cultured in RPMI 1640 medium with L-glutamine supplemented with 100 U/mL penicillin, 100 U/mL streptomycin, and 10% human type AB serum. These cells were stimulated with 100 ng/mL soluble anti-CD3 Ab plus 100 ng/mL anti-CD28 Ab, or 50IU Cry j 1 and Cry j 2, for 8hours. After culture, cells were collected and incubated with anti–CD4–fluorescein isothiocyanate and phycoerythrin-conjugated IL-10 secretion antibody. Immunophenotypic analysis was performed by using a Becton Dickinson FACScan instrument and cell sorting by using a FACS Aria cell sorter (Becton Dickinson, Mansfield, Mass). The Tr1 population was gated (gate 1) as shown in Fig 1, *B*. When PBMCs were stimulated with CD3/CD28 antibodies, these 2 sorted populations showed similar expression of TGF-β compared with non-Tr1 cells (gate 2) on the basis of quantitative PCR or intracellular staining with anti–TGF-β antibody in normal controls (Fig 1, *C and D*). Subsequently, cellular proliferation was evaluated. PBMCs (10^6/mL) were first labeled with 10 μmol/L carboxyfluorescein succinimidyl ester and stimulated with Cry j 1 and Cry j 2 as discussed. After 4 days of culture, PBMCs were stained with peridinin-chlorophyll-protein complex-conjugated anti-CD4 antibody, and the percentage of $CD4^+$ lymphocyte proliferation was measured. The proliferation was significantly suppressed in patients receiving SIT compared with patients with pollen allergy (Fig 1, *E*). This suppressive effect was neutralized by the addition of 2μg/mL anti–IL-10 antibody or anti–IL-10 receptor antibody, confirming that the suppression of reactivity against cedar pollen in patients receiving SIT is IL-10–dependent (for the proliferation assay, see Methods in this article's Online Repository). The percentage of circulating Tr1 cells ($IL\text{-}10^+CD4^+$T cells/$CD4^+$T cells) was significantly decreased in untreated patients with allergy compared with normal controls, and the level was increased in patients receiving SIT compared with untreated patients with allergy (Fig 1, *F*). This elevation of Tr1 cells in SIT-treated patients was observed when PBMCs were stimulated not only with Cry j 1 and Cry j 2 but also with CD3/CD28 antibodies, and this may be 1 reason why some patients undergoing immunotherapy for Japanese cedar pollen showed reduced sensitivity to other allergens. We also performed phenotypic characterization of the identified Tr1 cells by flow cytometry; interestingly, Tr1 cells showed more skin and gut–homing tendency than the non-Tr1 population (see this article's Fig E1 on the Online Repository at www.jacionline.org).

We next performed complementarity-determining region 3 size spectratyping analysis by using established β-variable primers to investigate the diversity of the T-cell receptor repertoire in the Tr1 populations expanded or changed by immunotherapy.[7,8] Total RNA was extracted from the sorted Tr1 population, and cDNA was prepared as previously reported.[7,8] Fig 2 shows a representative spectratype from Tr1 cells taken

from SIT-treated patients. Although the Tr1 population percentage was increased, a Gaussian distribution of complementarity-determining region 3 lengths could be observed in many BV subfamilies examined, except for oligoclonal expansion (2-4 peaks in spectratyping) in some BV subfamilies, indicating preservation of a highly diverse T-cell receptor repertoire (see this article's Fig E2 in the Online Repository at www.jacionline.org for spectratypes from other population).

Tr1 cells can be generated in the presence of locally produced IL-10 released from Tr1 cells.[4] Tr1 cells block cellular proliferation not via cell-to-cell contact but via cytokine-mediated mechanisms (eg, IL-10). The results of the current study may explain the mechanism of suppression against multiple allergens induced by epitope-specific immunotherapy in patients with pollinosis. Specific immunotherapy blocks the allergen specific IgE and induces an allergen-specific IgG response, which is induced by IL-10 from Tr1 cells.[2,3]

In conclusion, IL-10–producing Tr1 cells induced by specific immunotherapy play multifunctional roles in suppressing allergic reactions. We have shown here that patients undergoing specific immunotherapy have increased IL-10–producing Tr1 cell populations with high T-cell repertoire diversity, suggesting that this therapy induces tolerance to multiple allergens.

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Serum tryptase levels in atopic and nonatopic children

To the Editor:

The serum neutral mast cell protease tryptase is widely used as a marker of mast cell activation and clonal expansion. An increase in serum tryptase values above normal baseline measurements can be used to document an episode of systemic anaphylaxis. An increase in tryptase values that persistently exceeds 20 ng/mL in the absence of systemic allergic reactions constitutes a minor diagnostic criteria for mastocytosis. Normal reference values for serum mast cell tryptase have been established in the healthy adult population and range from 1 to 15 ng/mL, with an average of approximately 5 ng/mL,[1] and serum tryptase values between atopic and nonatopic adults are not different.[2] However, no comparable reference standards for children were found by using an all-inclusive PubMed search for articles published in English on serum tryptase values.

The aims of this study were thus to establish normal serum tryptase values in the pediatric population, to determine whether there are any differences in tryptase values in atopic versus nonatopic children, and to analyze tryptase values based on sex, race, ethnicity, total IgE level, weight, weight percentile, and dermatitis status.

In pursuit of these goals, we determined the tryptase values in 197 consecutive children (age range, 6 months to 18 years) presenting to the Pediatric Allergy Clinic at the National Institutes of Health, Bethesda, Maryland, for evaluation of allergic symptoms between July 2005 and August 2008. The patients were categorized as either nonatopic (n = 44) or atopic (n = 153), according to the presence of allergic symptoms and a tendency to produce IgE antibodies, as indicated by increased total IgE levels, specific IgE testing (ImmunoCAP; Pharmacia, Uppsala, Sweden), or cutaneous prick testing to commonly encountered environmental allergens.[3] None of the patients had a documented history of Hymenoptera venom allergy or a concurrent illness that would cause an increase in tryptase values nor could we identify a confounding effect of therapies used on tryptase values.

Serum tryptase values were obtained at the initial visit and determined by using a commercial fluoroenzyme immunoassay (Pharmacia ImmunoCAP 100) with a detection range of 1 to 200 ng/mL (undiluted) as performed by Mayo Medical Labs, Rochester, Minnesota.

Statistical analysis used the Wilcoxon rank sum test, the Kruskal-Wallis test, and the Spearman correlation coefficient. For the atopic and nonatopic groups, 95% prediction intervals of tryptase values were estimated, assuming a log-normal distribution.

Fig 1, *A*, shows the 95% prediction intervals and median of tryptase values. There was no statistically significant difference between nonatopic subjects and atopic subjects (median, 3.44 vs 3.56 ng/mL; $P = .93$; 95% prediction intervals, 0.64–6.77 and 0.98-10.80, respectively). Because these data were not normally distributed, nonparametric statistical analysis was performed based on the median (Wilcoxon rank sum test). The

METHODS

Antibodies and reagents

Ficoll was purchased from Sigma (St Louis, Mo), and the IL-10 secretion assay kit was from Miltenyi Biotec (Auburn, Calif). Cell surface staining buffer contains 0.1 mol/L PBS and 2% FCS (Biowest, Nuaillé, France). mAbs to CD4–fluorescein isothiocyanate, CD25-phycoerythrin, and forkhead box P3-phycoerythrin-Cy5 were purchased from eBioscience (San Diego, Calif). Antibody against TGF-β–peridinin-chlorophyll-protein complex was purchased from R&D (Minneapolis, Minn). The cells were stimulated with 100 ng/mL soluble anti-CD3 plus 100 ng/mL soluble anti-CD28 (BD Biosciences, San Jose, Calif), or 50 IU Cry j 1 and Cry j 2 (Torii, Tokyo, Japan). Cells were cultured in a final volume of 200 μL RPMI 1640 medium with L-glutamine supplemented with 5 mmol/L HEPES, 100 U/mL penicillin, 100 U/mL streptomycin (Invitrogen, Carlsbad, Calif), and 10% FCS.

Real-time quantitative PCR

RNA was isolated by using ISOGEN (Nippon Gene, Tokyo, Japan), according to the manufacturer's instructions. Total RNA 1 μg (A260/A280 = 1.7-2.0) was reverse-transcribed with oligo-dT primers and the SuperScript III First-Strand Synthesis System (Invitrogen) in a final volume of 20 μL. Quantitative real-time PCR was performed with a TaqMan by using ABI gene expression assays (Applied Biosystems, Foster City, Calif) according to the manufacturer's instructions. GAPDH was used as a control for cDNA input.

Proliferation assay

PBMCs (10^6/mL) were initially labeled with 10 μmol/L CFSE and then stimulated with 50 IU Cry j 1 and Cry j 2 with or without 2 μg/mL anti–IL-10 neutralizing antibody or anti–IL-10 receptor antibody (R&D) for 4 days. PBMCs were collected and stained with CD4-PerCP antibody (BioLegend, San Diego, Calif). Cell proliferation was analyzed by a CellQuest flow cytometer (Becton Dickinson, Franklin Lakes, NJ). The percentage of proliferative cells was calculated by dividing $CD4^+$ proliferative lymphocytes by the total number of $CD4^+$ lymphocytes (n = 10 per each population).

Statistical analysis

Statistical analysis was performed by using the Kruskal-Wallis nonparametric ANOVA test with *post hoc* analysis with the Dunn multiple comparison test. A *P* value less than .05 was considered statistically significant.

Complementarity-determining region 3 spectratyping analysis

T-cell receptor BV segments were amplified with 1 of 43 BV subfamily-specific primers and constant-variable primer recognizing both CB1 and CB2 regions. The sequences of BV primers and fluorescent CB primer have been previously described.[E1,E2] PCR products were applied to a 5% polyacrylamide sequencing gel, and the size distribution of each fluorescent PCR product was determined by electrophoresis on an automated 377 DNA sequencer (Applied Biosystems). In this technique, an amplified TCR BV subfamily migrates as a series of bands, each one corresponding to a different complementarity-determining region 3 length separated from one another by 3 nucleotides. Data were analyzed by using the GeneScan software (Applied Biosystems), which assigns a size and peak area to the different PCR products.

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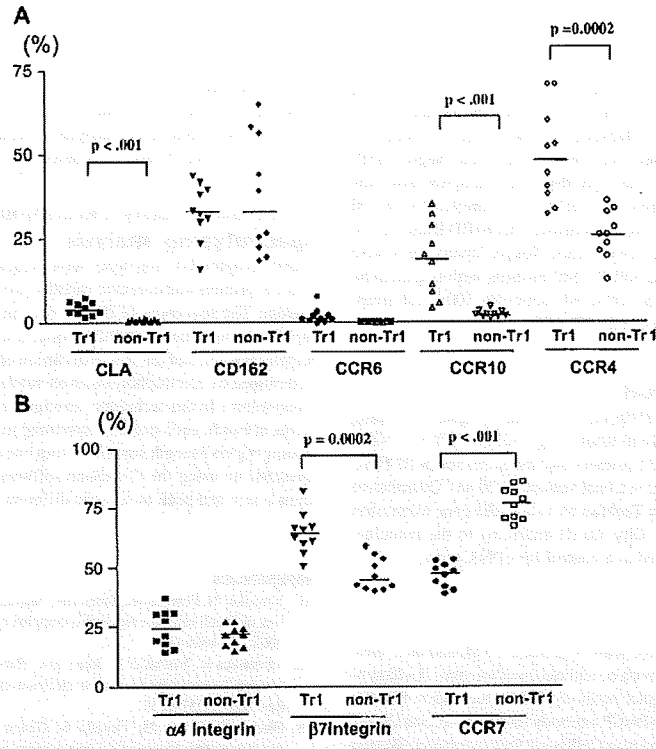


FIG E1. Phenotypic characterizationof identified Tr1 cells. $CD4^+$ T cells were purified from normal PBMCs and cultured with CD3/CD28 antibodies for 8 hours as described in the text. We analyzed the expression levels of skin-homing receptors and chemokine receptors (cutaneous lymphocyte-associated antigen *(CLA)*, a sialyl $Lewis^x$-related epitope expressed on P-selectin glycoprotein ligand 1, CCR6, CCR10, and CCR4), as well as gut (α4 and β7 integrins) and lymph node (CCR7)–homing receptors on $CD4^+$ T cells. Levels of the skin-homing markers CLA, CCR10, and CCR4 were elevated in the Tr1 population compared with the non-Tr1 population. The expression level of β7 integrin was also increased in the Tr1 population, but the levels of the lymph node marker CCR7 were decreased (n = 10, Mann-Whitney test).

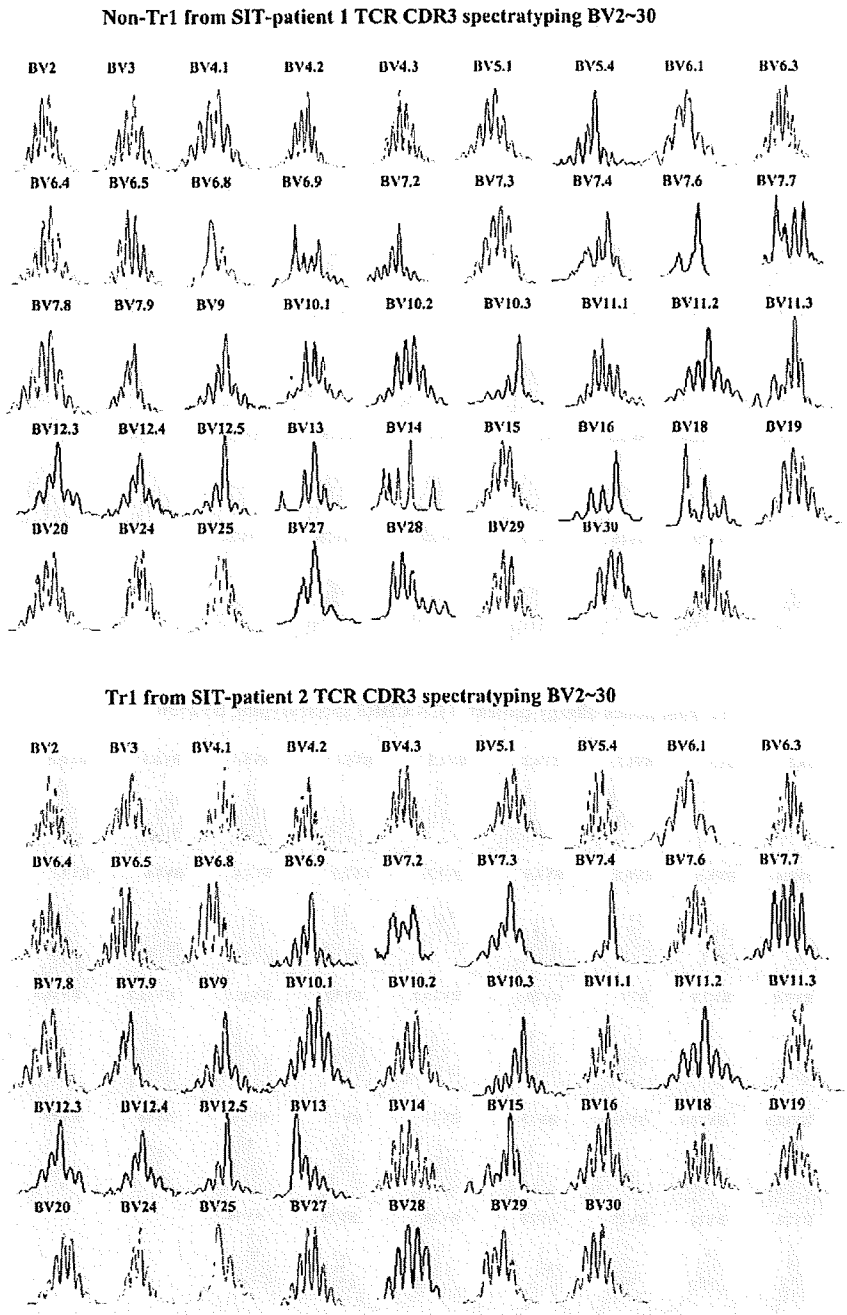
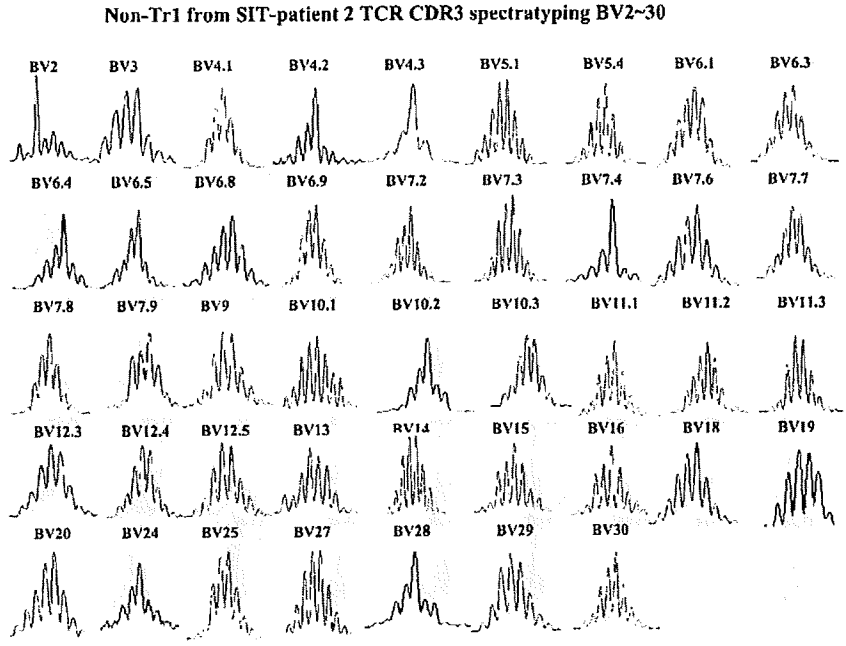


FIG E2. T-cell receptor complementarity-determing region 3 (CDR3) size spectratyping analysis of Tr1 or non Tr1-population from SIT-patient, pollen allergy-patient, or normal control.



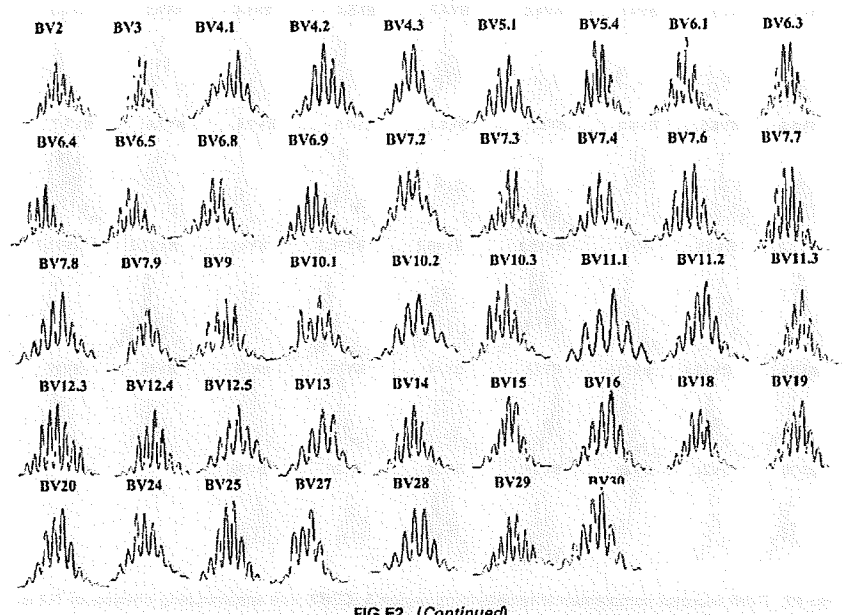
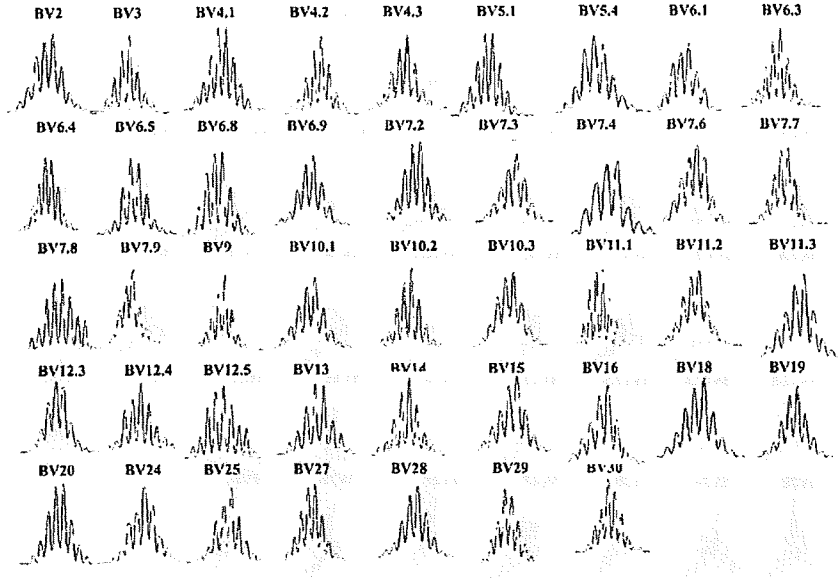


FIG E2. (*Continued*)

non-Tr1 from pollen allergy-patient TCR CDR3 spectratyping BV2~30



Tr1 from normal control TCR CDR3 spectratyping BV2~30

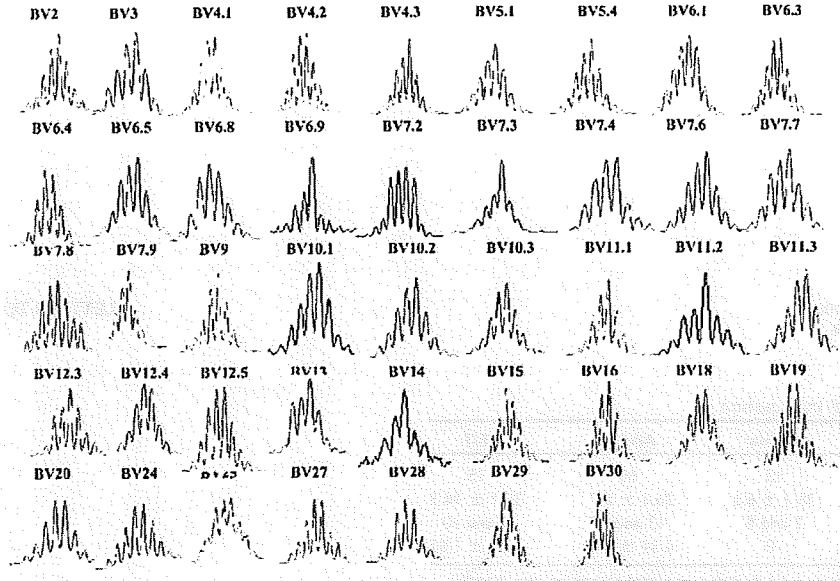


FIG E2. (*Continued*)

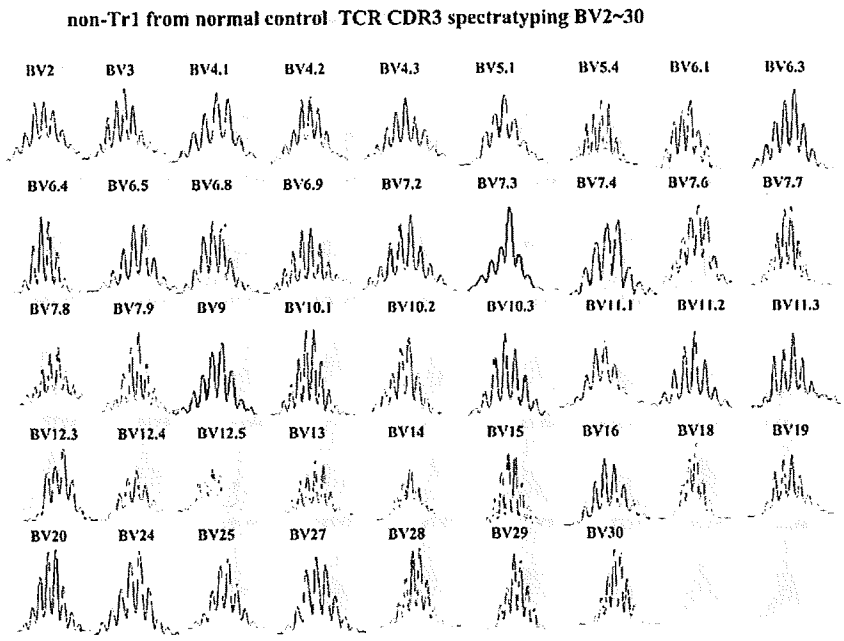


FIG E2. (*Continued*)

TABLE E1. Patients' information

	Normal	Allergy	SIT
N	13	60	15
Age (y)	38.4 ± 6.1	26.8 ± 5.7	39.1 ± 14.5
Male and female	7 and 6	43 and 17	5 and 10
TNSS	0	4.34 ± 1.61	2.21 ± 1.85

Nasal symptoms of sneezing, nasal discharge, and nasal congestion were recorded every day. Symptoms were categorized on a 5-point scale (0, none; 1, mild; 2, moderate; 3, severe; 4, extremely severe) according to practical guidelines for the management of allergic rhinitis in Japan. The average of total nasal symptom score *(TNSS)* for the 3 nasal symptoms in the cedar pollen season of February and March 2008 was calculated.[E3]

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原　著

スギ花粉症有病率の地域差について

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【目的】我が国におけるスギ花粉症の有病率は馬場の2008年の調査により[1]，平均26.5%とされているが各地域の有病率には大きな差が存在する．これまで，中村[2]，Okuda[3]らによって全国のスギ花粉症有病率の調査が行われてきたが，主に抗体陽性率や発症率との観点から分析が行われており，わずかにOkudaによって飛散花粉数と有病率の関係が述べられているにとどまっている．大気汚染との関連では特定地域における調査はあるが全国的な解析はほとんどないのが現状である．本研究では花粉数，大気汚染，気象条件など外部条件が，地域間の有病率にどの程度影響を与えているかについて検討を行った．
【方法】馬場の調査による各都道府県のスギ花粉症有病率[1]と各地域の平均花粉数，花粉の飛散期間，2月および3月の湿度，SPM，NOx，Oxなどについて相関を求め，有病率の差に関与する因子を検討した．花粉数についてはスギおよびヒノキ科花粉の合計値とスギ，ヒノキ科に分けた場合についても検討した．相関の高い因子については1998年と2008年の有病率の差について同様の結果になるかを検討した．
【結果】有病率と最も相関が高くなったのは花粉の飛散期間で，次いで花粉数，湿度の順であった．1998年と2008年の有病率の増加に関与したと考えられる因子は同様に花粉飛散期間，花粉数，湿度の結果であった．SPMなどの大気汚染に関しては有意な関係は見られなかった．湿度に関しては森[4]らの調査による高湿度におけるダニ増殖の影響とは異なる結果になった．

Key words: humidity —— pollen disperse period —— total amount pollen

はじめに

スギ花粉症に関する全国的な疫学調査はきわめて例が少なく，2001年の奥田による調査[3]，および，1998年および2008年の馬場，中村，中江によるものだけである[1][2][5][6]．本研究では馬場の調査による各都道府県別のスギ花粉症有病率の地域差が何に起因するものかを調べた．馬場の調査は，全国の耳鼻咽喉科医とその家族を対象としたアンケート調査であり，サンプル集団に偏りがあることから無作為の調査ではないが，奥田による調査との相関の高さ，また，耳鼻咽喉科医という専門職による判定という面からもある程度の信頼性は確保されていると考えられる．調査は2008年1

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利益相反（conflict of interest）に関する開示：著者全員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．
Abbreviations: NOx "concentration of nitrogen oxide", Ox "concentration of oxidants", SO_2 "concentration of sulfur dioxide", SPM "concentration of suspended particulate matter"
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Table 1 The prevalence of cedar-pollen allergy according to region

Region	2008	1998	Increase	Region	2008	1998	Increase
Hokkaido	2.2	2.9	− 0.7	Shiga	26.4	12.5	13.9
Aomori	12.5	11.9	0.6	Kyoto	32.8	16.7	16.1
Iwate	12.1	9.4	2.7	Osaka	25.2	14.9	10.3
Miyagi	32.5	21.3	11.2	Hyougo	20.5	11.2	9.3
Akita	14.0	8.2	5.8	Nara	35.0	14.3	20.7
Yamagata	25.0	23.1	1.9	Wakayama	20.3	17.4	2.9
Fukushima	26.4	13.8	12.6	Tottori	24.4	11.4	13.0
Ibaraki	25.6	20.4	5.2	Shimane	13.1	14.1	− 1.0
Tochigi	39.6	22.0	17.6	Okayama	19.1	11.5	7.6
Gunma	31.9	19.2	12.7	Hiroshima	27.8	16.7	11.1
Saitama	39.6	24.8	14.8	Yamaguchi	27.3	16.5	10.8
Chiba	32.4	20.1	12.3	Tokushima	28.8	13.4	15.4
Tokyo	32.1	20.4	11.7	Kagawa	21.5	13.9	7.6
Kanagawa	33.1	18.1	15.0	Ehime	28.3	21.1	7.2
Niigata	15.0	11.3	3.7	Kouchi	41.2	25.7	15.5
Toyama	17.4	8.4	9.0	Fukuoka	18.2	11.2	7.0
Ishikawa	20.5	9.3	11.2	Saga	26.3	19.4	6.9
Fukui	21.6	13.4	8.2	Nagasaki	15.2	8.0	7.2
Yamanashi	44.5	26.9	17.6	Kumamoto	13.6	10.3	3.3
Nagano	25.0	25.9	− 0.9	Oita	22.7	14.4	8.3
Gifu	36.5	21.0	15.5	Miyazaki	8.2	11.6	− 3.4
Shizuoka	39.3	25.3	14.0	Kagoshima	12.1	4.7	7.4
Aichi	28.0	17.5	10.5	Okinawa	6.0	0.6	5.4
Mie	33.2	24.8	8.4				

月に全国の耳鼻咽喉科医9656名に年齢，性，居住する都道府県と住環境，スギ花粉症，通年性アレルギー性鼻炎，スギ以外の花粉症の有無などについてアンケート調査を行ったもので，1998年の調査もまったく同様の方法であった．アンケート発送数9656通のうち，転居などで返送されたものが54通であり，実際の送付数9602通に対し，回答があったのは3621通，回収率37.7%であった．アンケート調査の結果をTable 1に示す．全国平均で通年性アレルギー性鼻炎の有病率が23.4%，スギ花粉症の有病率が26.5%，スギ以外の花粉症有病率が15.4%，花粉症全体の有病率が29.8%，アレルギー性鼻炎全体の有病率が39.4%であった．スギ花粉症の有病率および花粉症全体の有病率は1998年の調査に比較して10%あまり増加しており，他が5%前後の増加であるのに対して極めて高い伸びを示した．北海道と沖縄を除く地域でスギ花粉症の有病率を見ると最も高い山梨県の44.5%から最も低い宮崎県の8.2%までばらつきが非常に大きくなっている（Table 1）．

Table 2 Matrix of correlation coefficient

	①	②	③	④	⑤	⑥	⑦	⑧	⑨
cedar-pollen-allergy	1.00	0.95*	0.14	0.14	0.16	0.06	0.01	− 0.58*	0.60*
pollen-allergy		1.00	0.11	0.24	− 0.11	0.03	0.04	− 0.55*	0.51*
PAR			1.00	0.08	0.03	0.17	− 0.19	0.12	− 0.35
SPM				1.00	0.27	0.19	0.44	− 0.20	− 0.13
SO_2					1.00	0.21	0.19	0.08	0.15
NOx						1.00	0.18	0.07	0.13
Ox							1.00	0.17	0.25
humidity								1.00	− 0.28
pollen									1.00

① cedar: prevalence of cedar-pollen allergy
② pollen-allergy: prevalence of whole pollen-allergy
③ PAR: Prevalence of Perennial Allergic Rhinitis
④ SPM: concentration of suspended particulate matter
⑤ SO_2: concentration of sulfur dioxide
⑥ NOx: concentration of nitrogen oxide
⑦ Ox: concentration of oxidants
⑧ humidity: monthly average humidity in February
⑨ pollen

方 法

1. 花粉との関係

本研究では地域ごとの有病率の差がこのように大きくなる原因について調査を行った．解析の対象は北海道と沖縄を除く地域の有病率について，関与が予想される因子として，地域の平均花粉数の平方根，スギ花粉とヒノキ科花粉が分離されている地域では，それぞれ単独の花粉数との比較，シーズンの最大飛散数の平均値，花粉の飛散期間が特定できる地域では，飛散期間との関係を調べた．花粉数は環境省の委託調査を実施しているNPO花粉情報協会が所持する花粉データベースから各都道府県の県庁所在地のデータを用いた．解析にあたっては花粉データの無い沖縄とスギ花粉が極めて少ない北海道を除く東北から九州について行った．花粉数を実数ではなく平方根にしたのは，東京都花粉症対策委員会の調査[7]により，花粉症の症状との関係が実数より平方根または対数と比較した方が相関が高いからである．およそ60%の地域では，花粉の飛散開始から終了までの期間，シーズンの最大飛散数の比率が分かっており，同様に相関を求めた．スギ花粉とヒノキ科花粉が別に計測されている地点についてはスギ花粉とヒノキ科花粉合計値，スギ花粉単独，ヒノキ科花粉単独での相関も求めた．

2. 気象因子との関係

気象因子として2月および3月の平均湿度から空気の乾燥度合いと有病率の関係を，また，ダニの関与が全国レベルで影響を与えているかを夏の湿度から検証した．気象データは当該都道府県の気象台の観測値を用いた．

3. 大気汚染との関係

大気汚染物質としてデータは県庁所在地における環境省および自治体観測値の平均値を用い，3月のSPM，SO_2，NOx，Oxと花粉症有病率の関係を調べた．

4. 食生活との関係

内閣府の全国家計調査から牛乳，肉類，鶏卵，ヨーグルトの購入費と花粉症有病率の関係を調べた．

5. 有病率増加との関係

1から4の因子について有意な関係にあったものに

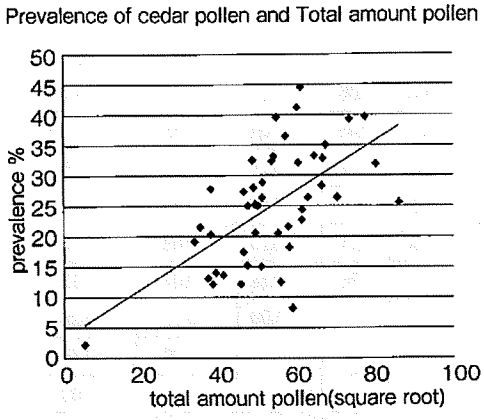

Fig. 1. There was a significantly positive correlation between the prevalence of cedar-pollen allergy and the square root of mean cedar pollen count in each region. The coefficient of correlation was 0.6. The longer pollen season, the severer all pollen allergy symptoms.

ついて，1998年の有病率，および2008年と1998年の有病率の差についても同様な関係が見られるかを調べた．

解析は線形回帰分析で行い，相関マトリクスを作成して，各因子間の内部相関を確認した．

結　果

1. 花粉との関係

スギ花粉症の有病率と各地の10年間の平均花粉数の平方根との関係を示したのがFig. 1である．Okuda[3]が過去に行った調査と同様の結果で，花粉数の平方根とスギ花粉症有病率の相関係数は0.6で，有意な関係であった．花粉観測において，スギ花粉とヒノキ科花粉を区別して観測している地域についてのみ，スギ花粉およびヒノキ科花粉単独での有病率との関係を調べると，相関係数はそれぞれ，0.35と0.39であり花粉数の合計よりも相関が低くなった．

他の因子として花粉の飛散数の最大値および花粉の飛散開始から飛散終了までの期間についても有病率との関係を検討した．飛散期間が明瞭であった地域は24地点であり[10]，すべての地域を網羅しているわけではないが，結果をFig. 6に示す．花粉飛散期間とスギ花粉症有病率の相関係数は0.76であり，検討した因子の中では最も相関が高くなった．

なお，通年性アレルギー性鼻炎と花粉数の相関係数は−0.35であり，花粉数とは逆相関になっていた．

2. 気象因子との関係

気象条件として花粉飛散初期の2月の平均湿度とスギ花粉症の有病率の関係をFig. 3に示す．相関係数は−0.58であり，湿度が低い地域ほどスギ花粉症の有病率が高いという結果であった．ちなみに通年性アレルギー性鼻炎と湿度の相関係数は0.12であり，スギ花粉症とは明らかに異なる結果であった．

3. 大気汚染との関係

次に大気汚染の指標となるSPMと有病率の関係をFig. 2に示す．図から明らかなようにSPMと有病率の間には関係は認められなかった．相関係数は0.14であった．

その他の大気汚染物質に関しても，SPM，SO_2，NOx，Oxいずれも有意な関係は見られなかった．

4. 食生活との関係

また，食生活では肉類，牛乳，ヨーグルトはいずれも相関はなく，鶏卵の摂取量でやや高くなっている．

花粉症全体と各因子との関係もスギ花粉症とほぼ同様の傾向を示すが，食生活でヨーグルトの摂取量が多い地域で相関がやや高かった．

5. 有病率増加との関係

各因子について計算した結果をTable 2に示す．スギ花粉症を中心に相関係数をみると最も高いのは花粉症全体であり，これは1998年からの増加率がほぼ一致していることから花粉症全体の中で占めるスギ花粉症の比率が非常に高いことを示している．有病率との関係では，最も相関が高いのは地域ごとの花粉数であり，次に2月の湿度であった．湿度と花粉数の間には有意な関係がなく，また，表にはないが年間の平均湿度や夏，秋の湿度との間には有意な関係は見られなかった．

次に，花粉数，湿度がスギ花粉症の有病率に本

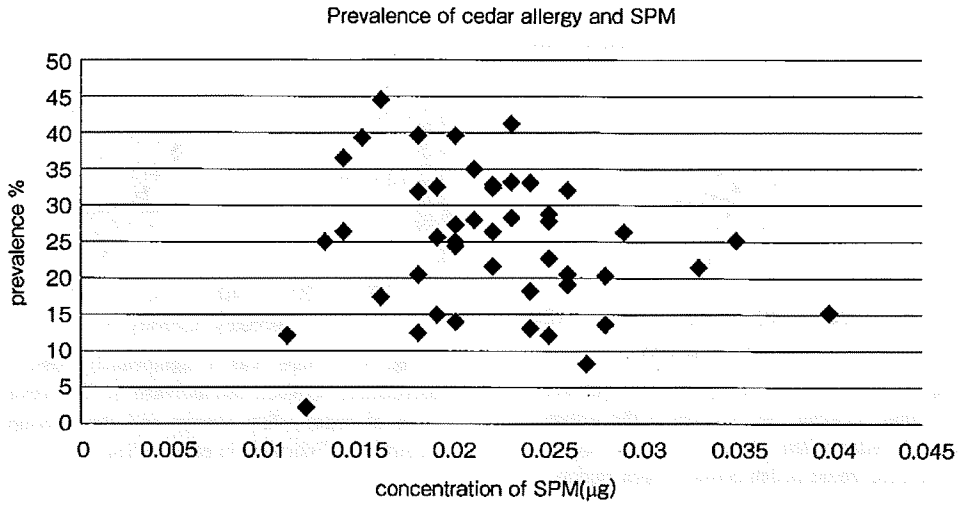

Fig. 2. There was no significant relationship between the prevalence of cedar-pollen allergy and the concentration of SPM.

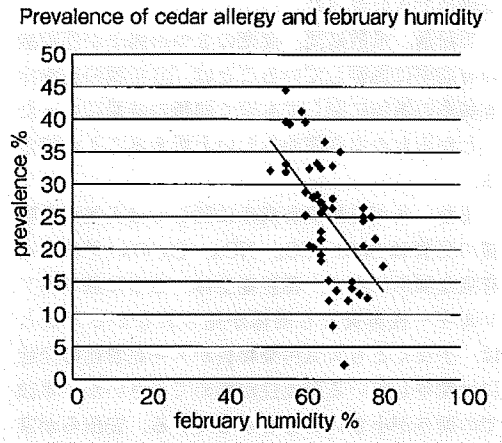

Fig. 3. There was a significantly positive correlation between the prevalence of cedar-pollen allergy and the average humidity in February.

当に関与しているかを確認するために，1998年と2008年におけるスギ花粉症有病率の差と花粉数，湿度および花粉飛散期間の関係を検討した．その結果をFig. 4，Fig. 5に示す．スギ花粉症の有病率の増加は花粉数および湿度ともに相関係数0.48であり，花粉数が多く，湿度が低い地域ほど有病率の増加が顕著であることが確認された．

また，1998年と2008年におけるスギ花粉症有病率の増加と花粉の飛散期間との相関は0.70であった．シーズンの最大飛散数の平均と有病率との相関は0.24であった．

なお，1998年におけるスギ花粉症有病率と各因子の相関係数は花粉数の平方根が0.51，湿度が−0.48，飛散期間が0.70，SPMが0.17，鶏卵購入量が0.29であった．

考　察

以上の結果からスギ花粉症の有病率の地域差は花粉の飛散期間，花粉数，春先の湿度が影響している可能性がかなり高いことが示唆された．花粉数よりも花粉の飛散期間の相関が高いことは，少量の花粉であっても，連続して暴露されることにより，抗体産生が持続することによるものではないかと考えられるし，過敏性の亢進につながる可能性もある．さらに花粉の飛散数が多ければ，抗体産生をより助長することになるのであろう．花粉の飛散量，飛散期間は花粉症発症に対してはインダクションフェーズとしての働きだけではな

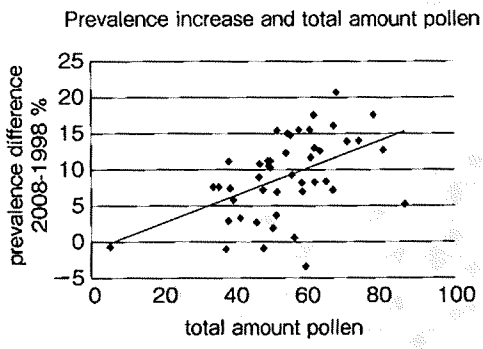

Fig. 4. There was a significantly positive correlation between the increase in the prevalence of cedar-pollen allergy and the square root of mean cedar-pollen count in each region.

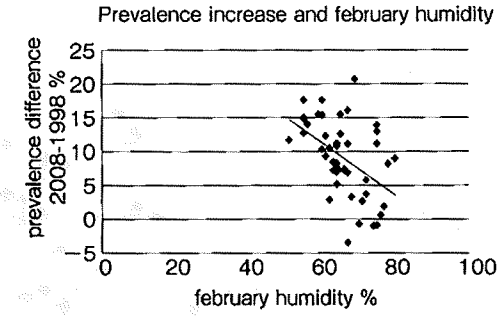

Fig. 5. There was a significantly positive correlation between the increase in the prevalence of cedar-pollen allergy and the average humidity in February in each region.

く，エフェクターフェーズとしても働いていると考えられ，特に飛散期間の長さは，繰り返しの刺激によっての効果が大きくなるのではないだろうか．スギ花粉とヒノキ科花粉を分けて解析した例は今までにないが，東京都における患者調査の結果[7]でもスギ花粉単独，あるいはヒノキ科花粉単独による相関よりも合計の花粉数においての方が，花粉数と患者動態の関係が明瞭になっており，本研究の結果もそれを裏付けるものになっている．

一方，湿度が低い場合には花粉症症状が悪化しやすいことは知られているが，湿度が低い地域ほどスギ花粉症の有病率が高いことは，乾燥化が進む都市部における花粉の再飛散の影響も考えられるが，花粉飛散時期の空気の乾燥が鼻粘膜に何らかの影響を与え，花粉由来の抗原が体に取り込まれやすくなるよりも，エフェクターフェーズとして，過敏性の亢進に働いているではないだろうか．

森らは栃木県における花粉症有病率の調査[4]で，一般家屋より集合住宅のスギ花粉症有病率が高いことに注目し，その原因を集合住宅内では密閉によって湿度が高くなり，結果としてダニの増加から低年齢におけるアレルギーの増加として説明している．しかし，日本においてダニの繁殖が最も盛んな7月および8月の湿度と地域ごとのスギ花粉症有病率の間には全く有意な関係はみられなかった．特定の地域内での調査ではダニの関与による影響は無視できないが，本研究のように日本全体の有病率の差を検討した場合には明瞭な差は検出できなかった．

花粉量，飛散期間，湿度の3つの因子が花粉症の有病率に影響していることは，10年間の花粉症有病率の増加に関しても全く同様の結果になったことからもかなり確からしいと考えることができる．

また，スギ花粉症有病率に関しては大気汚染物質の影響はSPM，SO_2，NOx，Oxのいずれでも有意な関係になく，花粉症全体，さらに通年性アレルギー性鼻炎でも関係が見られなかったことは，少なくとも大気汚染物質がスギ花粉症の発症には関与している可能性が極めて小さいか，単独での関与が小さいことを示している．安田らが京都府の職員を対象に行った調査[9]では居住地の大気汚染物質の内，SPMと窒素酸化物濃度において花粉症疑い群と非疑い群で，マン・ホイットニーのU検定では有意差が認められたとしている．しかし，筆者も参加した東京都のディーゼル車排出ガスと花粉症の関連に関する調査[8]では，アンケートのみではなく，医師の診断を受けて花粉症と診断された群と非花粉症群に分け，さらに個人サンプラーもつけてもらってデータを得たが，大気汚染物質と花粉症の間に有意なオッズ比はどの項目でも得られなかった．本研究の全国都道府県

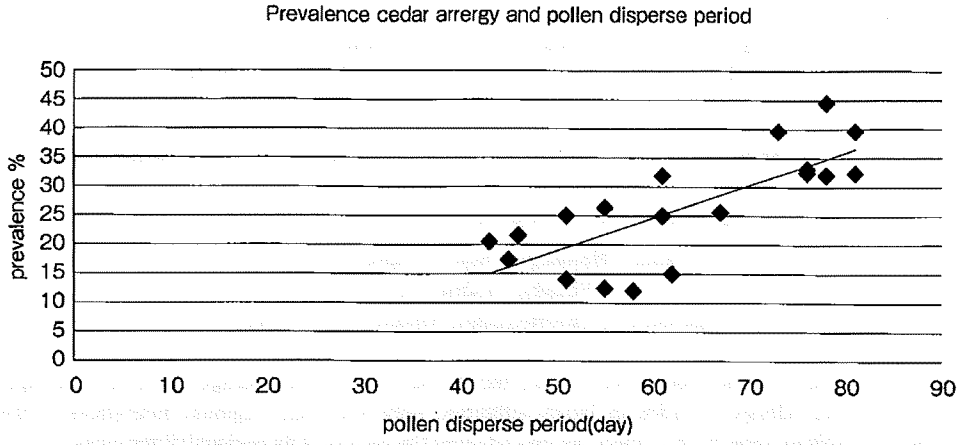

Fig. 6. There was a significantly positive correlation between the prevalence of cedar-pollen allergy and the average exposure to pollens.

別の有病率の差においても，少なくとも調査した大気汚染物質と花粉症の有病率の間には有意な関係は見いだせなかった．なお，通年性アレルギー性鼻炎と大気汚染物質との関係は，SPMではスギ花粉症よりやや高い相関になったが，有意ではなく，SO_2，NOx，Oxはいずれも相関係数が極めて小さくなっていた．

食生活に関しては，鶏卵で関与を疑わせる部分があるが，食生活は個人差，地域差が大きく，今回の検討では関与の度合いについて記述するほどの結果は得られなかった．食生活の中でヨーグルトは花粉症全体の有病率とやや高い相関が見られるが，ヨーグルトはSPMと逆相関になっており，これは大気汚染の低い地域，すなわち大都市以外でヨーグルトが多く摂取されていることを意味しており，イネ科花粉などその他の花粉が多くなっている可能性が考えられる．

本研究は地域ごとのスギ花粉症有病率とその差に影響する幾つかの因子を統計的に調べたもので，花粉飛散時期の乾燥がどのようなメカニズムで発症などに影響しているかは明らかではない．また，花粉の飛散量よりも花粉の飛散期間の相関が高いことも含めて，その原因に関しては今後の医学的な研究を待たねばならない．

なお，本研究はスギ花粉症の有病率の地域差について検討したものであり，花粉症症状の憎悪に関して，大気汚染などの関与を否定するものではない．

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