Cigarette smoking is associated with a greater risk of incident asthma in allergic rhinitis

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Background: Asthma and rhinitis are often comorbid conditions, and several studies have suggested that rhinitis often precedes asthma. Sensitization to allergen has been shown to be one of the strongest determinants of incident asthma, but little is known about the effects of cigarette smoking among individuals with allergic rhinitis.

Objective: We sought to evaluate the importance of cigarette smoking as an additional risk factor for incident asthma in a cohort of hospital-referred nonasthmatic adult subjects with allergic rhinitis.

Methods: The study population selected at baseline was invited for a follow-up visit 10 years later to check for possible asthma features. Categories of smokers, exsmokers, and never smokers were used in the analyses together with pack-years to calculate the level of cumulative exposure.

Results: Complete data were available from 325 patients. Smoking was significantly related to the risk of incident asthma, with the odds ratio (OR) being 2.67 (95% CI, 1.70-4.19) for univariate and 2.98 (95% CI, 1.81-4.92) for multivariate analyses. A clear dose-response association for exposure to tobacco and risk of new-onset asthma was observed in the multivariate analyses: those with 1 to 10 pack-years had an OR of 2.05 (95% CI, 0.99-4.27), those with 11 to 20 pack years had an OR of 3.71 (95% CI, 1.77-7.78), and those with 21 or more pack-years had an OR of 5.05 (95% CI, 1.93-13.20) compared with never smokers.

Conclusions: The current findings support the hypothesis that cigarette smoking is an important independent risk factor for the development of new asthma cases in adults with allergic rhinitis. (J Allergy Clin Immunol 2008;121:1428-34.)

Key words: Allergic rhinitis, asthma, cigarette smoking, cohort study, risk factors

Cigarette smoking is a modern-day epidemic that poses substantial health burden and costs. It is estimated that with well over 1 billion smokers worldwide, tobacco use is the chief avoidable cause of illness and premature mortality in the world. Cigarette smoking harms nearly every system of the human body, thus causing a broad range of diseases, many of which are fatal. In a 50-year prospective cohort study of more than 34,000 male British doctors, a remarkable difference in mortality rates between smokers and nonsmokers was observed, with an eventual risk of dying early that varied from about one half to about two thirds as a result of smoking.

Despite the plethora of evidence in illnesses such as cardiovascular diseases, cancer, and chronic obstructive pulmonary diseases (COPD), only limited information has been produced in relation to the role of cigarette smoking in respiratory allergies, with the exception of the widely reported increased risk of childhood asthma and wheezing in association with maternal and household smoking.

The effect of smoking on lung function and the progressive decrease in lung function in smokers with COPD has been known for a long time. More recent studies have shown that accelerated decrease in lung function over time is also present in asthmatic individuals who smoke. Adults and older children with asthma who are active smokers have more severe symptoms and worse asthma-specific quality of life compared with asthmatic nonsmokers, with asthma morbidity and mortality being reported to be greater in cigarette smokers with asthma compared with that in those who never smoked. More recently, a reduced therapeutic response to inhaled and oral corticosteroids in asthmatic patients who are cigarette smokers has been reported.

Cigarette smoking has been reported to be markedly associated with symptoms of chronic rhinitis and rhinitis has been shown to be an important risk factor for the development of asthma. Although sensitization to allergen has been shown to be one of the strongest determinants of incident asthma, little is known about the role of common modifiable risk factors, such as cigarette smoking, on the progression of rhinitis into asthma. Therefore we carried out a study in a cohort of clinic-referred nonasthmatic adult subjects with established allergic rhinitis to investigate the importance of cigarette smoking as an additional risk factor for incident asthma at 10 years’ follow-up.
METHODS

Study population
Medical records of patients with allergic rhinitis referred to the Outpatient Allergy Clinic of the University of Catania (Sicily) were reviewed. The subjects had to be between the ages of 18 and 40 years and not given a diagnosis of asthma at the time of referral (period between January 1990 and December 1991) to be included in the initial selection. The referred patients had to be born and residing in the province of Catania.

Our standardized diagnostic protocol at the time of referral consisted of case history, detailed smoking history, clinical examination, spirometry, and skin tests. Skin prick testing was performed on all subjects to determine sensitivity to common allergens (including *Parietaria judaica*, *Dermatophagooides pteronyssinus*, *Dermatophagooides farinae*, *Olea europea*, grass pollen, *Cupressus* species, *Alternaria* species, perennial rye, and cat allergen). We used 0.1% histamine solution as the positive quality control of the skin prick test and used the diluent media for allergens as the negative control. Skin prick test responses were regarded as positive if the mean wheal diameter was more than 3 mm.

The diagnostic criteria used for allergic rhinitis were those defined by the Joint Task Force on Practice Parameters in Allergy, Asthma, and Immunology and included watery rhinorrhea, nasal itch, sneezing, nasal blockage, and excessive lacrimation or conjunctival redness when exposed to allergens in combination with positive skin test reactions to suspected allergens. Records were excluded from the study if there was a past or present history of asthma, previous asthma symptoms, or asthma medication intake; abnormal spirometric values at the time of referral at baseline; or both. The possibility of unrecognized asthma in our study population was addressed by further reviewing the subjects’ case histories, and subjects were eligible for inclusion in the study only after at least 2 specialists in allergic diseases agreed they did not have any clinical history or symptoms suggestive of asthma. In addition, the absence of a diagnosis of asthma had to be documented in 3 consecutive control visits from the time of referral (usually within the subsequent 12 months from the time of referral). The criteria used to record a diagnosis of asthma were those based on the recommendations established by the American Thoracic Society.

Study design and explanatory and outcome variables
The present study took the form of a retrospective cohort study of subjects with allergic rhinitis. The records were selected from among the case notes of those patients referred to our allergy clinic in the period between January 1990 and December 1991 (baseline). Subjects seeking symptomatic relief were not excluded as long as they took over-the-counter medications (eg, topical decongestants, intranasal sodium cromoglicate, and/or oral antihistamines) on an occasional basis throughout the duration of this retrospective study. When nasal corticosteroids were prescribed, therapy had to be restricted to no more than 6 weeks per year. None of the subjects included had ever received allergen-specific immunotherapy at baseline. Details about their smoking histories were collected in addition to questions on the family history for atopic disease, second-hand smoke (SHS) exposure history, and pet ownership. Individual pack-years were calculated as follows:

\[
\text{Pack-years} = \frac{\text{Total number of years of cigarette consumption} \times \text{Total number of cigarettes smoked per day}}{20}.
\]

The study population selected at baseline (1990-1991) was then invited to the clinic in the period from January through April 2000 for a control visit to check for possible asthma features. In those cases in which a diagnosis of asthma could not be established with confidence, a methacholine challenge and a further clinical review were arranged 9 months later to improve diagnosis. On the same control visit, subjects were invited to complete a questionnaire on respiratory and allergic conditions (modified from the International Study of Asthma and Allergies in Childhood core questions), which included queries on the development of asthma symptoms and the need for drug therapy for rhinitis, asthma, or both, in addition to questions on changes in the clinical rating of rhinitis symptoms over the years.

Statistical methods
Explanatory variables were examined by using the \( \chi^2 \) test for patients who had asthma at follow-up versus those who did not have asthma.

Logistic regression was used to assess the predictability of the explanatory variables for subsequent development of asthma. The first logistic regression analysis univariately considered the explanatory variables of all subjects for whom smoking status was known at baseline. These variables included age (in years), sex, rhinitis symptoms (better vs not better), passive smoking (yes, no), presence of a house pet (yes, no), family history of atopy (yes, no), dichotomous smoking status (smoking vs nonsmoking), categorized smoking status (never smokers, former smokers [ie, individuals who were not smoking at the time of interview but have smoked at least 100 cigarettes in their lives], and current smokers), immunotherapy treatment (yes, no), and pack-years categories (0, 1-10, 11-20, and \( \geq 21 \) pack-years). Then a multivariate logistic regression analysis was performed on these subjects, with variables retained in a forward stepwise manner so long as the significance (P value) of entering variables was at least as small as 0.05. A P value for entering variables smaller than the conventional .05 was used to partially compensate for the multiple comparisons that arise when variable selection is performed.

The second logistic regression analysis was for stratified analyses according to immunotherapy treatment and sex. We assessed the association between smoking variables and asthma among those who received immunotherapy for their rhinitis compared with those who did not receive immunotherapy during the course of the study. We tested the interaction of smoking status and immunotherapy and smoking status and sex in relation to the development of asthma.

RESULTS
There were 325 patients for whom all explanatory variables and asthma status at follow-up were available (Fig 1). Table I presents the proportion of subjects who subsequently had asthma based on categorical explanatory variables and smoking status. The mean age for our population at baseline was 29.1 years, and according to smoking status, the mean age of never smokers was 28.6 years, of former smokers was 27.7 years, and of current smokers was 30.2 years. It is apparent that female subjects, those whose symptoms had not improved, those with a pet or exposure to passive smoking at home, and those with a family history of atopy were more likely to have asthma. Participants who received immunotherapy treatment were less likely to have asthma compared with those with no immunotherapy treatment. There was an apparently synergistic effect of these variables with respect to subsequent development of asthma among current smokers compared with never or former smokers.

The logistic regressions for all 325 patients are presented in Table II in univariate and multivariate analyses. Smoking status is presented in 2 ways. First, smokers (current or former) versus never smokers was significantly related to the risk of asthma in the univariate analyses (odds ratio [OR], 2.67; 95% CI, 1.70-4.19) and even more strongly related in the multivariate analysis (OR, 2.98; 95% CI, 1.81, 4.92). We also used the 3 categories of smoking status (current, former, and never smokers)
in a separate analysis. With never smokers as the reference group, we found, as expected, that current smokers were at higher risk than former smokers of asthma, and there was not a significant difference between never and former smokers in the development of asthma (Table II). The 3-category smoking status variable failed to enter the multivariate analysis, however, because the 2-category variable was more significant. Former smokers were not significantly different from never smokers, and the significance of the 3 category variable was driven by the active smokers.

The other significant variables in the univariate models were sex, improvement of symptoms, family history of atopy, and presence of a house pet. Age, exposure to passive smoke, and immunotherapy treatment were not significant. The results of the multivariate analysis, with the exception of family history of atopy, were similar to those for the univariate analysis, where smoking status, sex, improvement of symptoms, and exposure to a house pet were significant and included in the model. The ORs for the variables included in the multivariate model were little changed from their univariate values.

We then assessed pack-year categories (0, 1-10, 11-20, and ≥21) separately (where former smokers were excluded, n = 33) to test the dose-response association of exposure to tobacco and risk of asthma (Table III). In the multivariate analyses there was a clear dose-response association, with those with 1 to 10 pack-years having an OR of 2.05 (95% CI, 0.99-4.27), those with 11 to 20 pack-years having an OR of 3.71 (95% CI, 1.77-7.78), and those with 21 or more pack years having an OR of 5.05 (95% CI, 1.93-13.2) compared with those with 0 pack-years (never smokers). Symptoms and sex were the other significant risk factors and included in the final stepwise model.
Finally, we carried out stratified analyses according to sex and to the use of immunotherapy to assess whether the association between smoking and asthma was different based on these variables.

One hundred twenty-eight participants with allergic rhinitis did not receive immunotherapy, whereas 197 did receive it. Compared with never smokers, the multivariate risk of asthma for smokers with allergic rhinitis who did not receive immunotherapy was an OR of 3.73 (95% CI, 1.72-8.08); having a pet in the house was the only other significant risk factor. For smokers who received immunotherapy treatment, the multivariate OR for having asthma was lower at 2.62 (95% CI, 1.34-5.10). Similarly, the association between smoking and asthma among current smokers was higher for women (OR, 3.67; 95% CI, 1.61-8.38) compared with that for men (OR, 2.74; 95% CI, 1.36-5.52; Table IV). Results of the test of interaction for smoking status and sex were statistically significant ($P < .0001$). This was consistent after excluding former smokers. For former smokers, men were more likely to have asthma compared with men who were nonsmokers, but this was not significant for female former smokers. For pack-year categories, the sample was small, and most results had wide CIs.

### DISCUSSION

To the best of our knowledge, this is the first study that addressed the association between cigarette smoking and asthma among adults with allergic rhinitis. Our results suggest that smoking is strongly predictive of the development of new-onset asthma in adults with allergic rhinitis. Using multiple variables of smoking exposure, we found a consistently positive association between smoking and asthma. There was a dose-response association with increasing exposure to tobacco. Furthermore, immunotherapy attenuated this association. Other significant risk factors for the development of asthma were female sex and nasal symptoms that had not improved. In particular, female smokers were more likely to have asthma compared with male smokers. In addition, there was a smaller excess progression to asthma among those exposed to passive smoking and a house pet and among those with a positive family history for allergic diseases compared with their complements.

It is now well documented that rhinitis frequently precedes the onset of asthmatic symptoms and acts as an important risk factor, but there remains a lot to be learned about the role of cigarette smoking on the progression of rhinitis into asthma. Cigarette smoking is common in adults with rhinitis, with prevalence...
The epidemiologic evidence for the association between smoking and asthma is conflicting. Active cigarette smoking has been associated with the development of asthma in recent, but not in earlier, studies. However, these population studies mostly rely on questionnaires for the diagnosis of allergic rhinitis and asthma. Our study addresses other issues that might explain the heterogeneity of these epidemiologic studies, including examining asthma at ages when COPD is not prevalent, conducting regular prospective assessments of asthma and smoking, and considering the possibility that treatment modalities (especially regular nasal corticosteroids) might have acted as confounders.

Our study has the advantage of a relatively long follow-up period of 10 years. The cohort approach minimizes the possibility of reverse causality that might be encountered in case-control studies. Another advantage of this study is the rigorous clinical assessment of asthma diagnosis before exclusion at baseline and of its diagnosis as an outcome at the end of follow-up. Failing to diagnose actual asthma cases at baseline would have introduced systematic bias, which could affect the results by either increasing or decreasing the observed OR. On the other hand, missing the diagnosis of asthma at the end of follow-up would have attenuated the observed OR. The fact that the study subjects were examined by the same respiratory unit at baseline and at follow-up 10 years afterward is important for standardizing asthma diagnosis criteria in such a population. It is also important to obtain an accurate history of steroid and other asthma treatments during follow-up. Because intranasal use of corticosteroids has been shown to reduce asthma symptoms in patients with allergic rhinitis, we attempted to address these variables in our cohort, and there was no difference between asthmatic and nonasthmatic patients for these treatments.

A possible weakness of our study includes relying on medical records for the selection of the study subjects at baseline. However, all these subjects were examined and given careful medical diagnoses and documented in the clinic by allergy specialists. In relation to the rigor (or lack thereof) of the asthma diagnosis, it must be noted that the absence of bronchial hyperresponsiveness (BHR), peak expiratory flow monitoring, and reversibility to β-agonist data is not critical in the present experimental setting. It is well known that BHR is also present in patients with allergic rhinitis, and no clinical evidence of asthma. Moreover, the possibility of a transient increase in BHR after acute cigarette

### TABLE III. Logistic regression for the development of asthma: Continuing smokers and nonsmokers combined

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>df</td>
<td>χ²</td>
</tr>
<tr>
<td>Pack-years (4 categories)</td>
<td>3</td>
<td>20.7</td>
</tr>
<tr>
<td>1-10 vs 0</td>
<td></td>
<td>2.08 (1.07-4.04)</td>
</tr>
<tr>
<td>11-20 vs 0</td>
<td></td>
<td>3.87 (1.98-7.57)</td>
</tr>
<tr>
<td>≥21 vs 0</td>
<td></td>
<td>3.24 (1.35-7.76)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>1</td>
<td>1.8</td>
</tr>
<tr>
<td>Sex (male vs female)</td>
<td>1</td>
<td>23.3</td>
</tr>
<tr>
<td>Symptoms: better vs not better</td>
<td>1</td>
<td>24.1</td>
</tr>
<tr>
<td>Symptoms: better vs unchanged vs worse</td>
<td>2</td>
<td>24.9</td>
</tr>
<tr>
<td>Better vs worse</td>
<td></td>
<td>0.17 (0.07-0.45)</td>
</tr>
<tr>
<td>Unchanged vs worse</td>
<td></td>
<td>1.5</td>
</tr>
<tr>
<td>Passive smoke (yes vs no)</td>
<td>1</td>
<td>6.4</td>
</tr>
<tr>
<td>House pet (yes vs no)</td>
<td>1</td>
<td>4.4</td>
</tr>
<tr>
<td>Atopic family history (yes vs no)</td>
<td>1</td>
<td>3.5</td>
</tr>
</tbody>
</table>

Only significant (P < .01) variables are included in the multivariate analysis.

### TABLE IV. Logistic regression for development of asthma by sex

<table>
<thead>
<tr>
<th>Variable</th>
<th>Men</th>
<th>n</th>
<th>OR (CI)</th>
<th>Women</th>
<th>n</th>
<th>OR (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smokers vs nonsmokers</td>
<td>2.74 (1.36-5.52)</td>
<td>3.67 (1.61-8.38)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Former smokers vs nonsmokers</td>
<td>3.82 (1.30-11.3)</td>
<td>0.99 (0.30-3.28)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smokers vs nonsmokers</td>
<td>2.74 (1.36-5.52)</td>
<td>3.76 (1.63-8.68)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pack-years by categories</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-10 vs 0</td>
<td>2.10 (0.76-5.79)</td>
<td>2.06 (0.72-5.85)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>11-20 vs 0</td>
<td>2.14 (0.82-5.57)</td>
<td>11.2 (2.34-53.3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥21 vs 0</td>
<td>6.29 (1.91-20.7)</td>
<td>3.17 (0.71-14.2)</td>
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<td></td>
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</tbody>
</table>

The only included covariate is symptoms (better vs not better). Only current smokers and nonsmokers are included in the last 2 analyses.

rates similar to those found in the general population, and in the present work we show that it is an important risk factor for the development of new-onset asthma cases among those with rhinitis. In particular, the intensity of smoking appears to be associated with the strength of the association because a clear dose-response effect of smoking exposure (assessed as pack-years) for stronger association with a risk of new-onset asthma was observed in our study population. This underscores the notion that cigarette smoking is an important risk factor for the development of new asthma cases among those with rhinitis and no clinical evidence of asthma. Moreover, the observed OR. The fact that the study subjects were examined and given careful medical diagnoses and documented in the clinic by allergy specialists. In relation to the rigor (or lack thereof) of the asthma diagnosis, it must be noted that the absence of bronchial hyperresponsiveness (BHR), peak expiratory flow monitoring, and reversibility to β-agonist data is not critical in the present experimental setting. It is well known that BHR is also present in patients with allergic rhinitis, and no clinical evidence of asthma. Moreover, the possibility of a transient increase in BHR after acute cigarette
smoking might represent an additional confounding factor for which adequate correction would be required, thus making evaluation of BHR by methacholine inefficient in the current experimental setting. BHR was investigated when a possible diagnosis of asthma was in doubt. By adopting this strategy, a diagnosis of asthma could not be established with confidence in 39 subjects at the end of follow-up, and these subjects were excluded from the study. In addition, reversibility to β-agonists was not assessed because it was anticipated that the majority of patients with rhinitis would have had normal lung function (by means of inclusion criteria in the study, FEV1 ≥80%).

It is unclear why a large proportion of individuals with allergic rhinitis who smoke eventually progress to bronchial asthma. Subclinical inflammatory changes are known to be present in the lower airways of subjects with allergic rhinitis (even in the absence of clinical asthma), and these can lead to the development of asthma over subsequent years. It is likely that persistent exposure to airborne allergens and cigarette smoke in combination might have an additive or synergistic effect. Tobacco smoke is a complex mixture of gases and vapors, and the particulate phase possesses an adjuvant effect that might favor development of allergen-specific IgE antibodies and IgE-mediated allergic airway diseases. Laboratory studies in human subjects and animals have shown that the polyaromatic hydrocarbons (eg, anthracene, fluoranthene, pyrene, and phenanthrene) present in the particulate phase of cigarette smoke and diesel fumes have the ability to induce allergic immune responses and enhance allergic inflammation. Because formation of allergen-specific IgE antibodies is a key event in the process of the development of airway allergy and in sensitized individuals increases the risk of allergic rhinitis and asthma, progression to bronchial asthma in individuals with allergic rhinitis is likely to be expected in those who smoke regularly. Irritant substances in tobacco smoke might also have the ability to induce chronic inflammation in the airways and BHR; the combined effect of increased BHR and active airway inflammation could potentially set the stage for an enhanced risk of asthma.

We also found that the positive association between smoking and the greater risk of incident asthma was attenuated by immunotherapy. The reason for this is not known, but it is possible that immunotherapy might hinder disease progression through the induction of CD4+CD25+FOXP3+ regulatory T cells that attenuate allergen-specific T(H)2 cell responses. We did not observe an association of SHS exposure and enhanced risk of asthma in never smokers. Incomplete classification of SHS exposure is likely to limit our ability to examine this association because we did not collect information on exposure in social situations (eg, workplace SHS exposure) that might be a major contributor to SHS exposure. Given the incomplete assessment of SHS exposure, the lack of association with greater risk of incident asthma should not be overinterpreted.

Our results have important clinical implications. Individuals with allergic rhinitis who smoke will be more likely to have asthma, and quitting might confer some potential clinical benefit in terms of long-term prevention of asthma. Furthermore, immunotherapy for allergic rhinitis can decrease the risk of asthma, even among smokers. Decreasing the exposure to tobacco products is a public health imperative and more so for subjects with allergic rhinitis. Physicians have the responsibility to alert their patients with allergic rhinitis about the additional risk they have if they smoke. Prospective studies of new-onset asthma are now needed to clarify the association between regular cigarette smoking and greater risk of incident asthma.

We thank Professor N. Crimi (Director of the Outpatient Allergy Clinic of the University of Catania) for helpful assistance in providing access to the medical records. We also thank all of the doctors involved in the compilation of patients’ medical records: F. Armato, I. Ciamarra, C. Maccarrone, S. Magri, C. Mastruzzo, L. V. Milazzo, R. Oliveri, C. Pagano, B. Palermo, F. Palermo, G. Paolino, V. Picciolo, G. Prosperini, G. Pulvirenti, D. R. Raccuglia, G. Santonocito, I. Settinieri, and C. Vancheri.

Clinical implications: Physicians have the responsibility to alert their patients with allergic rhinitis about the additional risk of asthma if they smoke and to engage in smoking cessation interventions.

REFERENCES
