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Italian Multicenter Cross-Sectional Study (AISAG) on light smoking and allergic diseases in adults

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KEY WORDS

Smoking; allergic respiratory diseases; food allergy; allergic dermatitis

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Summary

Allergic rhinitis, allergic dermatitis, and food allergy are extremely common diseases and are frequently associated to each other and to asthma. Smoking is a potential risk factor for these conditions, but so far, results from individual studies have been conflicting. On the basis of these contradictory data in the literature we have carried out a multicenter cross-sectional study to evaluate the relationship between some allergic conditions and exposure or not to active light smoking. The study was carried out between May 2013 and November 2013 in 22 different Italian hospitals. Patients with respiratory and/or food allergy, and aged 18 years and over, visited at Allergy Outpatient Clinics, were invited to participate. A total of 1586 allergic patients (21.6% smokers) with a mean age of 39.2 years (standard deviation, SD = 15.1) were included. We demonstrated that the prevalence of tobacco smoking was higher in patients with food allergy and in asthmatic patients in stage III-IV. But no other statistical differences were found at univariate analysis. The sensitization patterns of non-smokers and smokers were similar. Furthermore, tobacco smoking was associated with higher risk of food allergy and lower risk of asthma. Moreover, tobacco smoking was an independent risk factor for persistent respect to intermittent rhinitis, and for asthma GINA stage III-IV with respect to stage I-II.

Introduction

Population-based studies appear to show a relationship between smoking and bronchial hyperresponsiveness. However, the presence of asthma in adults has generally been unrelated

to smoking history, possibly reflecting a false opinion about the tendency for asthmatics not to become regular smokers or to smoke less than their non-asthmatic counterparts (1). Several studies have demonstrated that active smoking increases the risk for developing asthma (2-5).

But there are also scattered studies that seem to cast doubt on the relationship between exposure to cigarette smoke and asthma / allergies. For example, it was reported that IgE levels in smokers showed a moderate inverse correlation with the degree of smoking and that the mean IgE level in ex-smokers was much lower than in current light smokers but was still higher in nonsmokers (6). It was also demonstrated that cigarette smoking is associated with high prevalence of chronic rhinitis and low prevalence of allergic rhinitis in men (7). On the basis of these contradictory data in the literature we have carried out a multicenter cross-sectional study to evaluate the relationship between some allergic conditions and exposure or not to active light smoking.

Methods

The study was carried out between May 2013 and November 2013 in 22 different Italian hospitals. Patients with respiratory and/or food allergy, and aged 18 years and over, visited at Allergy Outpatient Clinics, were invited to participate. Patients were asked about their smoking habit; non-smokers and light smokers (defined as 5-10 cigarettes per day for 5-10 years) were included in the study. The local Ethics Committee approved the study design and protocol and patients gave written informed consent.

For each subject, we collected data on age, gender, smoking habit, allergic symptoms, the pattern of respiratory sensitization, the presence of food allergy and atopic dermatitis. Asthma severity and control, and rhinitis severity were scored according to the Global Initiative for Asthma (GINA) and the Allergic Rhinitis and its Impact on Asthma (ARIA) Guidelines, respectively.

Skin prick tests (STPs) were done using a panel of standardized commercial extracts of allergens of the most common ones responsible for respiratory symptoms in Italy: pollens (*Graminaceae mix 5*: grass; *Compositae mix*; *Parietaria mix*: pellitory; *Betula pendula*: birch; hazelnut; olive, cypress), house dust mites (HDM: *Dermatophagoides pteronyssinus* and *D. farinae*), animal danders (dog, cat), feathers mix, moulds (*Alternaria alternata*, *Aspergillus fumigatus*, *Cladosporium herbarum*, *Penicillium mix*).

Serum specific IgEs were detected by currently available commercial laboratory methods (RAST and ImmunoCAP; Pharmacia AB, Uppsala, Sweden, then Phadia AB, now Thermo Fischer Scientific).

Patients were divided into two groups according to tobacco smoking: non-smokers and light smokers. Common statistical methods were used for the analysis of proportions and associations between tobacco smoking and demographic and clinical features. Furthermore, multivariate logistic regression models, adjusted for covariates, were used to investi-

gate associations of tobacco smoking (independent variable) with allergic symptoms, food allergy, atopic dermatitis and the pattern of respiratory sensitization (dependents variable). Results are presented as odds ratios (OR) and 95% confidence intervals. The selection of variables for fitting the most parsimonious model was performed using a backward stepwise procedure, with $p = 0.10$ for retaining each variable in the model.

Statistical analysis

For statistical tests, P values lower than 0.05 were considered significant in two-tailed tests. All statistical analysis were carried out using STATA, version 12.0, software (STATA Statistics/Data Analysis 12.0 - STATA Corporation, College Station, TX, USA).

Results

A total of 1586 allergic patients (21.6% smokers) with a mean age of 39.2 years (standard deviation, SD = 15.1) were included. The majority of them were aged 35 years or less. Asthma was present in 72.2% of subjects, rhinitis in 79.4% and United Airways Disease (rhinitis plus asthma) in 47.6%. Most of asthmatic were in GINA stage I and II (89.9%), whereas among patients with rhinitis, 57.6% had intermittent symptoms. The most common respiratory allergenic sensitizations were, in decreasing order: grass (62.9%), HDM (53.3%), Betula (29.6%) and Parietaria (25.0%).

The demographic and clinical features according to smoking habits are shown in **table 1**. The proportion of tobacco smokers was significantly higher in males, subjects younger than 45 years, non-asthmatic patients, and those with persistent rhinitis. In addition, the prevalence of tobacco smoking was higher in patients with food allergy and in asthmatic patients in stage III-IV, next to statistical significance threshold. No other statistical differences were found at univariate analysis. The sensitization patterns of non-smokers and smokers were similar, as shown in **figure 1**; this was confirmed when we restricted the analysis to monosensitized patients (**figure 2**).

After adjusting for demographic and clinical features, tobacco smoking was associated with higher risk of food allergy (OR = 1.46, CI 95%: 0.97-2.19; $p = 0.069$) and lower risk of asthma (OR = 0.75, CI 95%: 0.57-0.99; $p = 0.042$). Moreover, tobacco smoking was an independent risk factor for persistent respect to intermittent rhinitis (OR = 1.51, CI 95%: 1.16-1.96; $p = 0.002$), and for asthma GINA stage III-IV respect to stage I-II (OR = 1.73, CI 95%: 1.09-2.74; $p = 0.021$). No associations were observed between tobacco smoking and other clinical characteristics in multivariate logistic regression models.

Table 1 - Demographic and clinical characteristics according to tobacco smoking.

Variables	Categories	Non-smokers n (%) ¹	Smokers n (%) ¹	Total n (%) ¹	P value ²
Total		1243 (78.4)	343 (21.6)	1586	
Gender	Male	687 (55.3)	143 (41.7)	830 (52.3)	< 0.001
	Female	556 (44.7)	200 (58.3)	756 (47.7)	
Age (years)	32 ≤	428 (34.4)	128 (37.3)	556 (35.1)	0.010
	33-44	375 (30.2)	123 (35.9)	498 (31.4)	
	≥ 45	440 (35.4)	92 (26.8)	532 (33.5)	
Family history of allergy	No	877 (71.9)	241 (70.9)	1118 (71.7)	NS
	Yes	342 (28.1)	99 (29.1)	441 (28.3)	
Asthma	No	326 (26.3)	111 (32.4)	437 (27.6)	0.025
	Yes	915 (73.7)	232 (67.6)	1147 (72.4)	
GINA criteria (restricted to patients with asthma)	I-II	801 (90.7)	197 (86.8)	998 (89.9)	0.080
	III-IV	82 (9.3)	30 (13.2)	112 (10.1)	
Rhinitis	No	967 (77.6)	282 (22.4)	1258 (79.4)	NS
	Yes	267 (81.6)	60 (18.4)	327 (20.6)	
ARIA classification (restricted to patients with rhinitis)	Intermittent	581 (59.6)	143 (50.9)	724 (57.6)	0.009
	Persistent	394 (40.4)	138 (49.1)	532 (42.4)	
Polysensitization	No	405 (32.6)	112 (32.7)	517 (32.6)	NS
	Yes	838 (67.4)	231 (67.3)	1069 (67.4)	
United airways disease	No	646 (52.0)	183 (53.7)	829 (52.4)	NS
	Yes	596 (48.0)	158 (46.3)	754 (47.6)	
Atopic dermatitis	No	1164 (93.9)	319 (93.5)	1483 (93.8)	NS
	Yes	76 (6.1)	22 (6.5)	98 (6.2)	
Food allergy	No	1136 (91.6)	302 (88.6)	1438 (91.0)	0.082
	Yes	104 (8.4)	39 (11.4)	143 (9.0)	

¹Column percentage,²Chi square test. NS: Not statistical significant

Figure 1 - Pattern of the sensitizations (skin test positive) between non-smokers and smokers.

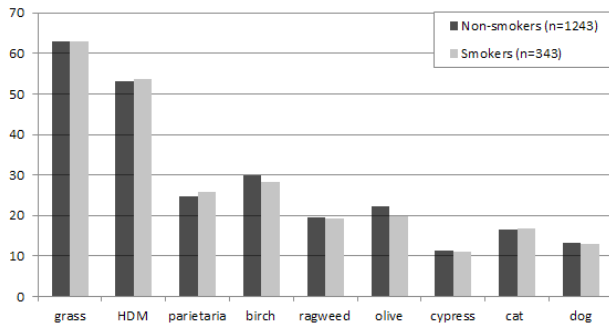
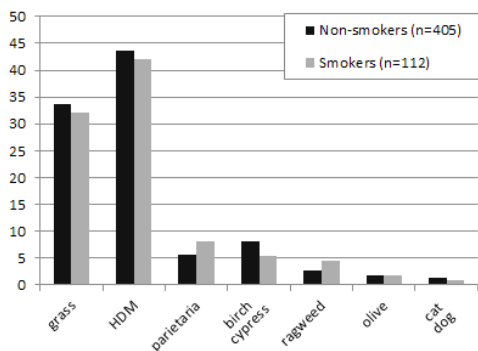


Figure 2 - Pattern of the sensitizations (skin test positive) between monosensitized non-smokers and smokers.



Discussion

Allergic rhinitis, allergic dermatitis, and food allergy are extremely common diseases and are frequently associated to each other and to asthma. Smoking is a potential risk factor for these conditions, but so far, results from individual studies have been conflicting. Prevalence rates for smoking in asthma are relatively close to those found in the general population and several studies have demonstrated that active smoking increases the risk for developing asthma (8-10). A 1996 longitudinal study of 5801 people born in 1958 who were part of a national British cohort has implicated smoking in the development of wheeze and asthma in young adults (8). Subjects were followed up at the ages of 7, 11, 16, 23, and 33 years. Active smoking was strongly associated with the incidence of asthma and wheezing illnesses between the ages of 18 and 33 (OR = 4.42, 95% CI 3.31-5.92)

after controlling for a variety of factors, including gender, maternal age, birth order, gestational age, hay fever, eczema, father's social class, and maternal smoking. In addition, among the 880 children who developed asthma or wheezy bronchitis by age seven, relapse at age 33 after prolonged remission of childhood wheezing was more common among current smokers. A study of adolescents found that those who smoked ≥ 300 cigarettes per year had a relative risk of 3.9 for developing asthma, compared to their non-smoking peers (9).

There is also a growing body of evidence that secondhand smoke exposure is associated with the development of asthma in early life (10). Maternal smoking is the most important cause of secondhand smoke exposure, because of the greater exposure of the child to the mother than the father (11-13).

In adults, data on the effects of environmental tobacco exposure on nonmalignant lung disease are sparse. The association between passive exposure to tobacco smoke and respiratory symptoms was studied in a sample of 4197 non-smoking adults as part of the Swiss Study on Air Pollution and Lung Diseases in Adults (SAPALDIA Study) (14). Passive exposure to tobacco smoke was associated with increases in the risks of doctor-diagnosed asthma (odds ratio = 1.39), wheezing, bronchitis, and dyspnea.

Prenatal exposure to smoking may also be important, being associated with reduced pulmonary function in the infant. One study, for example, evaluated the effect of prenatal maternal cigarette smoking on the pulmonary function of 80 healthy infants shortly after birth (15). Maternal smoking was assessed by questionnaire reports and urine cotinine concentration at each prenatal visit. Pulmonary function (assessed as flow at FRC) was lower in infants whose mothers smoked compared to those whose mothers did not smoke. Another report evaluated the effect of early levels of lung function on the subsequent occurrence of a wheezing lower respiratory tract illness in the first year of life (16). Reduced pulmonary function early in life increases the risk for wheezing and subsequently for asthma later in life. It has been proposed that prenatal smoking exposes the fetus to the growth-retarding effects of tobacco and enhances airway-parenchymal dysanapsis (disproportionately small airways compared to the size of the pulmonary parenchyma). These changes may contribute to the postnatal expression of increased airway responsiveness and asthma (17).

Two other studies have examined the effects of prenatal and postnatal exposure to smoking on asthma and wheezing in children (18-19). The first study used a broad case definition to identify 620 schoolchildren aged seven to nine years in Cape Town with current asthma or wheeze in the last 12 months (18). In bivariate analyses, maternal smoking, whether defined as ever smoking (OR = 1.80), smoking during pregnancy (OR = 1.97), smoking during the first year of the child's life (OR = 1.70), or

current smoking (OR = 1.70) was significantly associated with current asthma/wheeze among the children. The number of cigarettes smoked daily by the mother and the number of household smokers were also related to current asthma/wheeze. Further strengthening these findings, the children's cotinine-creatinine ratio was significantly associated with current asthma/wheeze (OR = 1.61 for the highest quartile versus the lowest quartile). In a multivariate logistic regression model controlling for a variety of known risk factors, maternal smoking during pregnancy (OR = 1.87, 95% CI 1.25-2.81) and the number of household smokers (OR = 1.15, 1.01, 1.30) remained significantly associated with current asthma/wheeze. The second study examined the relationship between current and past exposure to maternal, paternal, and non-parental environmental tobacco smoke in the home and several measures of asthma and wheeze in a large sample of school-aged children (11,534 children) from 24 communities in the US and Canada (19). Asthma was identified based on either an active diagnosis of asthma or use of medication for asthma. Wheeze outcomes were: any wheezing, wheezing with a cold, wheezing without a cold, persistent wheeze, shortness of breath with wheeze, awakening at night by wheezing, wheezing with exercise, medication for wheeze, emergency department visit for wheeze, and hospitalization for wheeze. Children who were currently exposed had a significantly increased risk of reported wheeze with a cold (OR = 1.65), emergency department visit for wheeze (OR = 1.63), persistent wheeze (OR = 1.42), shortness of breath with wheeze (OR = 1.35), wheeze with exercise (OR = 1.24), and medication for wheeze (OR = 1.23) in past year. For most of the wheeze outcomes, there was an increasing risk associated with increasing number of smokers in the home and number of cigarettes smoked in the home per day. Active asthma was significantly associated with exposure to environmental tobacco smoke in pregnancy only (OR = 2.70, 95% CI 1.13-6.45), and no significant association was found for currently exposed children.

Cigarette smoking and asthma interact to induce important adverse effects on clinical, prognostic and therapeutic outcomes (20-25). Active smokers, particularly females, are at risk of developing asthma. Smokers with asthma experience worse asthma control than nonsmokers with asthma. Mechanisms for the adverse effects of smoking in asthma include altered airway inflammation and corticosteroid insensitivity. Finally, in a recent systematic review and meta-analysis, it was observed very modest associations between smoking and some allergic diseases among adults (26). Among children and adolescents, both active and passive exposure to second hand smoke were associated with a modest increased risk for allergic diseases, and passive smoking was associated with an increased risk for food allergy. In our study we demonstrated that the prevalence of tobacco smoking was higher in patients with food allergy and in asth-

matic patients in stage III-IV. But no other statistical differences were found at univariate analysis. The sensitization patterns of non-smokers and smokers were similar. Furthermore, tobacco smoking was associated with higher risk of food allergy and lower risk of asthma. Moreover, tobacco smoking was an independent risk factor for persistent respect to intermittent rhinitis, and for asthma GINA stage III-IV respect to stage I-II. Additional studies with detailed measurement of exposure and better case definition are needed to further explore the role of smoking in allergic diseases. In conclusion, quitting smoking can improve symptoms and lung function, but the low rates of smoking cessation highlights the need for improved strategies for managing these patients. Clinical trials assessing new therapies for asthma need to enroll smokers to identify treatments that are effective in the asthma smoking phenotype.

Limits of the study

We are aware that our research may have an important limitation. The association between tobacco smoking and asthma could be affected by reverse causality bias: subjects with asthma are less inclined to start smoking than not asthmatic subjects, and probably smokers tend to quit smoking at the onset of asthmatic symptoms. A prospective cohort study of subjects without asthma and/or allergy should be appropriate to disentangle this topic, though it requires large sample and long times of observation. Finally, we have not considered in the study the problem of "secondhand" smoke during pregnancy or in early childhood and the and its potential consequences in adulthood.

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