

Smoking, atopy, and laboratory animal allergy

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ABSTRACT This study examined data from three cross sectional surveys of 296 laboratory workers exposed to small mammals. Four indices of laboratory animal allergy were studied: symptoms suggestive of occupational asthma, symptoms suggestive of any occupational allergy, skin weals to animal urine extracts, and serum binding in radioallergosorbent tests with urine extracts. Pooled data from the three surveys showed an association between smoking and all indices except radioallergosorbent tests; the association was significant for symptoms of occupational asthma. One of the three surveys consistently showed a stronger association of allergy indices with smoking than with atopy (defined on skin tests with non-animal aeroallergens). Associations with smoking persisted after stratifying by atopic status, suggesting that smoking may be a risk factor for laboratory animal allergy.

Smoking is associated with asthma caused by enzyme detergents¹ and snow crabs,² with skin weals to *Bacillus subtilis*³ and coffee bean,⁴ and with serum IgE antibody against ispaghula⁴ and tetrachlorophthalic anhydride (TCPA).⁵ This suggests that smoking is a risk factor for occupational allergy, possibly by increasing mucosal transport of antigen.^{5,6} The study of TCPA workers showed a statistically significant interaction between smoking and atopy (defined on skin tests with common aeroallergens): 16% of 31 atopic smokers had IgE antibody against TCPA, 12% of 111 non-atopic smokers, 8% of 36 atopic non-smokers but none of 98 non-atopic non-smokers.⁵ In animal experiments inhalation of tobacco smoke and other bronchial irritants potentiates sensitisation by inhaled antigen.⁷⁻⁹

Laboratory animal allergy (LAA) is common in research workers, who may show prevalence rates of over 40%.¹⁰ Atopy is associated with IgE antibody to animal allergens and with asthma caused by animals but less closely with nasal, eye, or skin symptoms when these are present without chest symptoms.¹⁰⁻¹³ To date, no relation between smoking and LAA has been identified. The survey of laboratory workers described in a companion paper found a slight excess of current smokers in those with symptoms suggestive of occupational asthma.¹⁰ We therefore examined data from this and two other populations to see if LAA is associated with smoking.

Methods

We have carried out cross sectional surveys of three populations occupationally exposed to animals. Survey A was of pharmaceutical research workers and is described in a companion paper.¹⁰ Survey B was of research workers at a tobacco company.¹⁴ The laboratory had been open only a short time and all but three workers who had ever worked there were seen and the original survey record forms were available. Survey C was of pharmaceutical research workers. A study by company staff has been published¹¹ and our survey gave similar results.¹⁵ The original forms were no longer available but some data were accessible on computer tape.

The self completed questionnaire in survey A has been described and LAA symptoms were defined as chest, nose, eye, or skin symptoms provoked by rats, mice, guinea pigs, or rabbits or which were temporally related to occupational exposure to animals, improving with reductions in exposure.¹⁰ Survey B used a similar definition in an interviewer administered questionnaire but included only rats, because only they were kept at the laboratory. An interviewer administered questionnaire was used at survey C and, apart from covering mice, guinea pigs, and rabbits as well as rats, was similar to that for survey B. The precise definition of LAA symptoms used to create the computer file on survey C was not clear so no data on symptoms are presented.

At surveys A and C, smoking history was noted by

Table 1 Subjects of surveys A, B, and C

Survey	A	B	C
Subjects*	133	23	140
Mean $\pm$ SD age (y)	32.3 $\pm$ 10.2	27.8 $\pm$ 8.9	33.0 $\pm$ 10.9
Mean $\pm$ SD employment (y)	8.7 $\pm$ 8.0	2.6 $\pm$ 1.7	8.1 $\pm$ 6.1
Female	41%	52%	24%
Current smoker	21%	39%	29%
Atopy	44%	30%	36%
LAA chest symptoms	11%	26%	—
Any LAA symptoms	44%	61%	—
Skin weal to urine extract	13%	48%	16%
Positive RAST to urine extract†	37%	—	30%

*Those who had skin tests.

†Percentage of 129 in survey A and of 126 in survey C.

questions from the Medical Research Council questionnaire.¹⁶ A smoker had smoked at least one cigarette a day for at least a year (or the equivalent in other tobacco products). An ex-smoker had not smoked for three months. Survey B noted current smoking status by different questions but with the same definitions.

All three surveys used skin prick tests, which were carried out by the same observer (ERH). At each, a 2 mm weal, after taking account of any response to a negative control solution, was taken as positive. Atopy was defined as at least one positive test to common, non-animal aeroallergens. These were B2 grass pollen mixture, *Dermatophagoides pteronyssinus*, and *Aspergillus fumigatus* (Bencard). Urinary extracts from rat, mouse, guinea pig, and rabbit were used in survey A¹⁰ and survey C. Survey B used only an extract of rat urine as exposure was only to rats.

Surveys A and C included radioallergosorbent tests

(RASTs) to measure serum IgE antibody concentration to urinary extracts from rat, mouse, guinea pig, and rabbit, which was expressed as percentage binding in survey A¹⁰ and as counts per minute (cpm) in survey C. A positive RAST in survey A was defined as at least the value which cut off the top 1% of an unexposed population, obtained from the *t* distribution of 20 unexposed referents, and was at least 1.2% for rat, 0.9% for mouse, 1.1% for guinea pig, and 1.0% for rabbit.¹⁰ Survey C results were compared with cord blood samples tested in the same assay and, for each urine extract, greater than 2000 cpm was regarded as positive.

Because of the known association between atopy and LAA¹⁰⁻¹³ and the interaction between atopy and smoking noted for serum IgE antibody to TCPA,⁵ LAA prevalence was examined by atopy and smoking. Ex-smokers were grouped with never smokers because the TCPA study suggested this grouping: for non-atopic individuals, the prevalence of IgE antibody of TCPA was nil in ex-smokers (as in the non-smokers) and for atopic individuals, intermediate between that of current and never smokers.⁵

Statistical analysis was by chi-squared and Fisher's exact tests and was aided by the software package Minitab (Pennsylvania State University). Statistical significance was assumed when $p < 0.05$.

Results

The populations are compared in table 1. A few subjects without skin test results were excluded. The short duration of employment in survey B was because the laboratory had opened recently. Eight of the 23

Table 2 Prevalence ratios of LAA indices for atopy and smoking

Index of LAA	Survey	Prevalence ratios*			
		Atopy		Smoking	
		Ratio	p†	Ratio	p†
LAA chest symptoms	A	4.8	0.005	2.1	0.156
	B	1.1	0.865	3.1	0.107
	C	—	—	—	—
	Pooled data	2.6	0.023	2.6	0.019
Any LAA symptoms	A	1.2	0.342	1.2	0.441
	B	1.3	0.497	1.6	0.184
	C	—	—	—	—
	Pooled data	1.2	0.332	1.3	0.139
Skin weal to urine extract	A	3.6	0.003	1.0	0.795
	B	1.3	0.555	3.1	0.021
	C	2.7	0.008	0.9	0.779
	Pooled data	2.1	<0.001	1.4	0.190
Positive RAST to urine extract‡	A	2.2	<0.001	0.9	0.638
	B	—	—	—	—
	C	2.2	0.003	1.2	0.516
	Pooled data	2.2	<0.001	1.0	1.000

*Ratio of prevalence of index in atopic subjects compared with non-atopic subjects and in current smokers compared with non-smokers.

†Two tailed p from chi squared.

‡RAST done in 129 in survey A and 126 in survey C.

Table 3 Prevalence of LAA symptoms by smoking and atopy

	Smokers			Non-Smokers			Total		
	LAC*	LAA*	(n)*	LAC	LAA	(n)	LAC	LAA	(n)
Survey A:									
Atopic	40%	60%	(10)	15%	46%	(48)	19%	48%	(58)
Non-atopic	6%	44%	(18)	4%	39%	(57)	4%	40%	(75)
Total	18%	50%	(28)	9%	42%	(105)	11%	44%	(133)
Survey B:									
Atopic	—	—	(0)	29%	71%	(7)	29%	71%	(7)
Non-atopic	44%	78%	(9)	0%	22%	(7)	25%	56%	(16)
Total	44%	78%	(9)	14%	50%	(14)	26%	61%	(23)

*Percentage with LAA chest symptoms (LAC) and with any LAA symptoms (LAA) in cell, denominator (n).

subjects no longer worked at the laboratory. In surveys A and C the subjects studied were currently employed in the laboratories.

Table 2 shows the ratios of the prevalence of LAA indices in atopic subjects compared with non-atopic subjects and in current smokers compared with non-smokers. All ratios for atopy were greater than one, indicating the expected association between atopy and LAA. Most ratios for smoking also were greater than one. The pooled data showed the expected significant associations between atopy and LAA chest symptoms, skin weals to urine extract, and positive RASTs. The pooled data also showed a significant association between smoking and LAA chest symptoms. Examining the ratios for individual surveys, atopy was consistently more closely associated than smoking with LAA in surveys A and C. Survey B gave different results, with smoking consistently more associated than atopy with LAA and, despite the small number in this survey, a significant association between smoking and skin weals to urine extract.

Tables 3, 4, and 5 present the prevalence of indices of LAA by smoking and atopic status, grouping ex- with never smokers for the reason stated above. The

pattern in the TCPA survey of the highest prevalence of sensitisation in atopic smokers and lowest in non-atopic non-smokers⁷ was seen in survey A, for LAA chest symptoms, any LAA symptoms, and skin weals. As the patterns suggesting interaction between atopy and smoking were not seen consistently and were not as striking as in the TCPA workers, statistical tests for interaction were not carried out. There were no atopic smokers in survey B, a finding unlikely to have occurred by chance ($p < 0.05$). For the non-atopic subjects, in whom the comparison could be made, all LAA indices measured were more prevalent in smokers and non-smokers ($p < 0.01$ for urine extract skin tests). The prevalence of LAA chest symptoms and of skin weals to rat urine extract was nil in non-atopic non-smokers in survey B, as for anti-TCPA IgE antibody in TCPA workers.

Discussion

It would not be surprising if smoking were associated with LAA as it is associated with a range of indices of sensitisation in both man and animals.¹⁻⁷ The prevalence ratios (table 2) and tables of prevalence by

Table 4 Prevalence of skin weal to urine extract by smoking and atopy

	Smokers		Non-Smokers		Total	
	Weal*	(n)*	Weal	(n)	Weal	(n)
Survey A:						
Atopic	30%	(10)	21%	(48)	22%	(58)
Non-atopic	6%	(18)	5%	(57)	5%	(75)
Total	14%	(28)	12%	(105)	13%	(133)
Survey B:						
Atopic	—	(0)	57%	(7)	57%	(7)
Non-atopic	78%	(9)	0%	(7)	44%	(16)
Total	78%	(9)	25%	(14)	48%	(23)
Survey C:						
Atopic	20%	(15)	31%	(36)	27%	(51)
Non-atopic	12%	(25)	9%	(64)	10%	(89)
Total	15%	(40)	17%	(100)	16%	(140)

*Percentage with skin weal to urine extract in cell, denominator (n).

Table 5 Prevalence of positive RAST to urine extract by smoking and atopy

	Smokers		Non-Smokers		Total	
	RAST*	(n)*	RAST	(n)	RAST	(n)
Survey A:						
Atopic	67%	(9)	51%	(47)	54%	(56)
Non-atopic	17%	(18)	27%	(55)	25%	(73)
Total	33%	(27)	38%	(102)	37%	(129)
Survey C:						
Atopic	36%	(14)	52%	(31)	47%	(45)
Non-atopic	33%	(24)	16%	(57)	21%	(81)
Total	34%	(38)	28%	(88)	30%	(126)

*Percentage with positive RAST to urine extract in cell, denominator (n).

atopy and smoking (tables 3–5) suggest that smoking is associated with LAA. There were small expected frequencies in some of the chi-squared tests carried out, so p values will be approximate but they were two tailed tests and therefore conservative, given our hypothesis that smoking is associated with LAA. Statistical tests on pooled data as well as individual studies were considered appropriate because of the generally consistent associations of LAA indices with atopy and smoking in the individual studies.

In surveys A and C atopy was consistently more closely associated than smoking with LAA. By contrast, smoking appeared to be a stronger risk factor than atopy in survey B. This was similar to our study of TCPA workers,⁵ where the prevalence ratios for anti-TCPA IgE were 5.8 for smoking and 1.9 for atopy. Also, survey B resembled the TCPA study in that the prevalence of LAA chest symptoms and of a skin weal to rat urine was nil in non-atopic non-smokers. There is a further similarity between the two populations: both had been exposed to an occupational antigen for a short period. The laboratory studied in survey B had opened only recently and the mean duration of employment was 2.6 years. In the TCPA exposed population TCPA was a new introduction to a manufacturing process and was first used about 2.5 years before the survey.^{5,17} By contrast, at the laboratories studied in surveys A and C, small animals had been used for many years and the mean duration of employment was over eight years at each. This suggests explanations for the greater association of smoking with LAA at survey B (which could also apply to the TCPA workers). Firstly, the effect of smoking may be to shorten the latent interval before LAA develops, so the association with smoking is seen in the first months or years of exposure but then weakens as the incidence of LAA in non-smokers approaches that of smokers. Most symptoms of LAA develop soon after exposure. For example, in Gross's cross sectional survey, 77% of the 59 cases of LAA developed symptoms in the first year of exposure and 95% in the first three years.¹⁸ Secondly, survey B may

have studied a more representative group than surveys A and C. This seems likely because all those who had ever worked at the laboratory were invited to participate and only three former employees were not seen. Two of the three were known to have left because of LAA. There was no information about the third. We can only speculate that these were atopic smokers and that their absence explains the significant deficit of atopic smokers in this population. Unfortunately there are no records of their smoking habits or atopic status.

We regard these observations as suggestive evidence that LAA is associated with smoking. The possibility requires further study, preferably by prospective surveys, noting atopy and smoking at first exposure to animals and estimating their effects on the incidence of LAA and on its latent interval.

We thank Mr D Gordon, Mr C Wale, Mr N Farrer, Dr T Lam, Dr P Baxter, Dr M Peters, Dr M Coe, Dr P Winter, Mrs J Hopkins, and Mrs A Zubeiri for help with survey A and Dr M Dally and Mrs P Vyas for help with survey C. We also thank the Camilla Samuel Fund for financial support for data analysis.

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