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Lower Prevalence of Positive Atopic Skin Tests in Lung Cancer Patients*

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Allergy prick skin testing was performed on 137 newly diagnosed patients with primary lung cancer and 137 age (± 3 years) and sex-matched randomly selected control subjects. We also compared 38 patients with lung cancer and 38 of their closest in age, same-sex siblings. Demographic data, personal, medical, smoking and occupational histories were obtained by personal interview. We skin tested these individuals with a standard battery of seven common allergens and a diluent control. Fewer patients (35.8 percent) than control subjects (58.4 percent) responded with one or more positive skin reactions ($p < .005$). There was no significant difference between patients (27.8 percent) and control subjects (37.2 percent) responding to more than one allergen. Fewer of the 38 sibling-matched patients had one

or more positive skin tests (23.7 percent) than did their siblings (55.3 percent) ($p < .01$). There were fewer patients with > 1 positive skin test (15.8 percent) than sibling control subjects (42.1 percent) ($p < .025$). There were no differences in smoking pack-years between patients and siblings. Historic evidence of allergy was greater in both control groups compared to their matched cancer groups; $p < .05$ for community controls, $p < .005$ for sibling control subjects. These findings raise the possibility that atopy, by either immunologic or nonimmunologic means, protects against development of lung cancer, or alternately, that lung cancer affects immunologic status as gauged by (type 1) skin sensitivity.

Previous studies¹⁻¹⁰ have indicated the possibility of a negative correlation between allergy-related disease and cancer. Most studies suggest that individuals with allergy-related disorders may be at decreased risk of cancer.¹⁻¹⁰ Decreased risks in patients with allergy-related diseases have been suggested in men for oral cancer, cancers of the lung, larynx, digestive system, urinary system and the cancers of all sites combined, and in women for cancers of the digestive system, reproductive system, cervix, and cancers of all sites combined. Difficulties with previous studies have included the suitability of control subjects, sample size, and the possibility that populations select themselves into smoking and nonsmoking groups on the basis of allergy-related conditions. Several other studies have found no protective relationship of an allergic history against development of cancer¹¹⁻¹⁴ and at least one¹⁵ has found a higher incidence of allergy associated with cancer.

In this study we have documented the clinical history of atopy and performed a battery of allergy prick skin tests on newly diagnosed untreated patients with primary lung cancer and two groups of control subjects: randomly chosen community control subjects and sibling control subjects.

METHODS

The study design, methodology and all correspondence were approved by the University of Saskatchewan President's Advisory Committee on Ethics in Human Experimentation. The records of the Saskatchewan Cancer Foundation were used to provide a profile of each patient with a diagnosis of primary lung cancer between November 1983 and March 1986. Interviews were conducted with patients, randomly selected community control subjects and familial control subjects. Questions relating to respiratory symptoms and smoking were modified from the British Medical Research Council Questionnaire. Pulmonary function tests and allergy prick skin tests were performed on those patients who were interviewed prior to surgery, chemotherapy or radiotherapy. A randomly selected community based control panel was generated with the cooperation of the Saskatchewan Hospital Services Plan data bank using age, sex and broad geographic area of the province as selection criteria. We tested each individual with a battery of seven common allergens (Hollister-Stier Division of Miles Labs, Ltd, Rexdale, Ontario) and a diluent control. The allergens used included house dust mite (1:100 wt:vol), mixed grain dust (1:10), mixed animal dander (cat 1:30, dog 1:30 and horse 1:30), mixed molds (*Alternaria* 1:60, *Aspergillus* 1:60, *Hormodendrum* 1:60, mixed weed pollen (1:20), mixed tree pollen (1:20) and mixed grass pollen (1:20). The wheal diameters were measured in two perpendicular directions at 10 minutes and the mean wheal diameter determined as the mean of the measurements. Data on 137 matched patient-community control pairs were analyzed. A second family-based control group was assembled using patient's siblings of the same sex and closest in age to the patient. Data on 38 matched patient-sibling control pairs were analyzed. We used the chi square technique to test the differences in distribution between exposure (smoking and occupational exposure), symptoms, conditions and prick skin tests and demographic variables between patients and control subjects.¹⁶

RESULTS

There was no difference between patients and ran-

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Table 1—Comparison of Demographic Variables

															Occupational Exposures											
	Gender				Age (years)																					
	Males		Females		≤50		51-60		61-70		71-80		>80		Grains*		Diesel Fumes		Weld-ing†		Asbestos		Arsenic			
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%		
Lung Cancer Patients and Randomly Selected Community Control Subjects																										
Patients	109	79.6	28	79.6	7	5.1	36	26.3	53	38.7	36	26.3	5	3.6	72	52.6	72	52.6	27	19.7	15	10.9	13	9.5		
Community controls	109	20.4	28	20.4	8	5.8	33	24.1	51	37.2	40	29.2	5	3.6	91	66.4	77	56.2	42	30.6	11	8.0	11	8.0		
	male/female 3.89						chi square = .45, df = 4, NS								*p<.01, †p<.05											
Lung Cancer Patients and Sibling Controls																										
Patients	24	63.2	14	36.8	6	16.2	7	18.9	16	43.2	8	21.6			16	42.1	14	36.8	7	18.4						
Sibling controls	24	63.2	14	36.8	6	15.8	8	21.1	16	42.1	8	21.1			18	47.4	18	47.4	8	21.0						
	male/female = 1.7						chi square = 1.1, df = 3, NS								NS											

domly selected community control subjects for the demographic variables of age, sex or residence on a farm or in a village, town or city. The two groups differed by educational level in that 9.5 percent of patients had post-secondary educational training vs 27.2 percent of control subjects ($p < .01$). There was a greater number of farmers in the control group than among the patients. Significantly more community control subjects reported occupational exposure to grains ($p < .01$) and welding ($p < .05$). The frequencies of exposure to diesel fuel, asbestos and arsenic were comparable (Table 1).

In response to the question, "Has your doctor ever

told you that you have _____?", similar frequencies of patients and community control subjects reported past histories of pleurisy (12.4 vs 9.5 percent), asthma (4.4 vs 7.3 percent), heart disease (18.2 vs 16.8 percent), arthritis (24.1 vs 32.1 percent), hayfever (4.4 vs 8.0 percent) and sinus trouble (27.7 vs 30.6 percent). Significantly more patients than randomly selected community control subjects reported morning cough ($p < .005$) and wheezing without a cold ($p < .005$). Fewer patients (21.9 percent) reported allergies than did the randomly selected community subjects (36.5 percent) ($p < .05$). A minority of the self-reported allergies in each group was to drugs. There was no difference in the

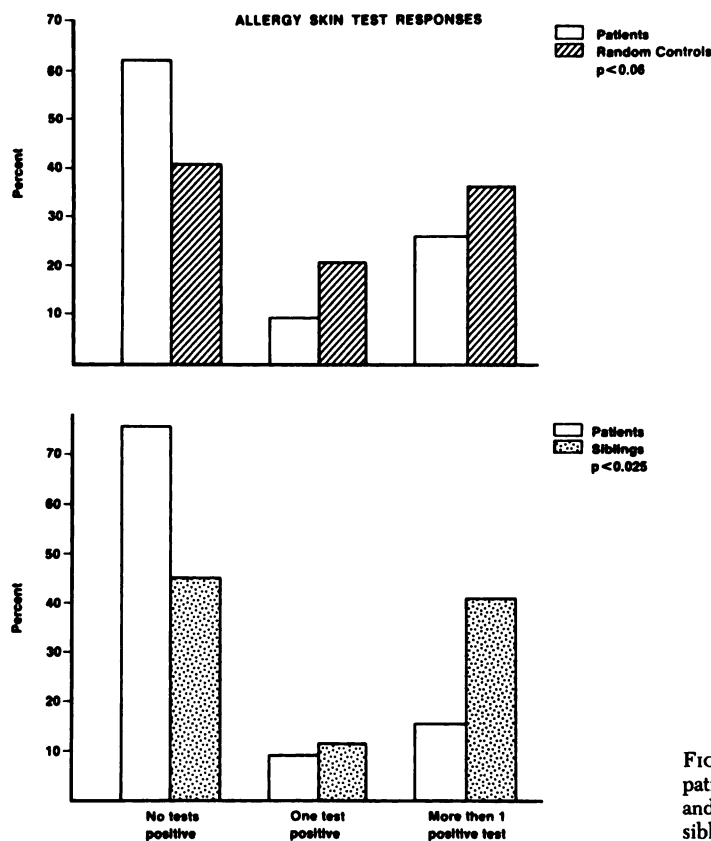


FIGURE 1. Distribution of allergy prick skin test responses in patients and in two groups of control subjects. *Upper panel:* patients and randomly selected control subjects; *lower panel:* patients and sibling control subjects.

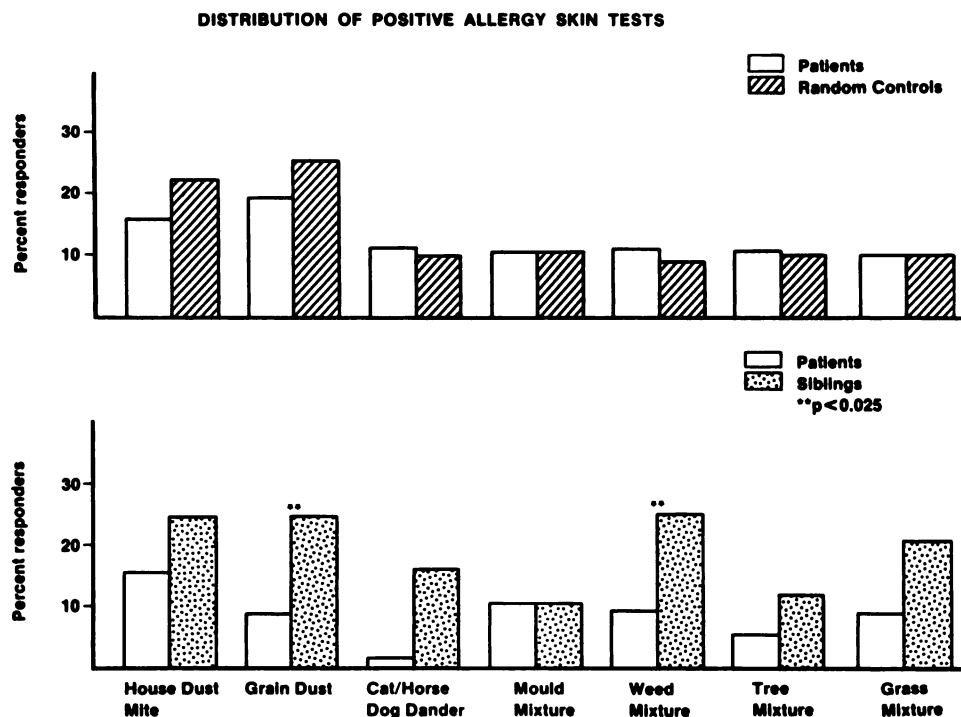


FIGURE 2. Distribution of positive allergy prick skin tests to individual allergens of patients with primary lung cancer and age- and sex-matched randomly selected community control subjects (*upper panel*) and patients with primary lung cancer and their same sex, closest-in-age siblings (*lower panel*).

reported frequency of rhinitis defined as the presence of a stuffy, runny or itchy nose for at least three months

per year for at least two consecutive years (13.9 vs 14.6 percent).

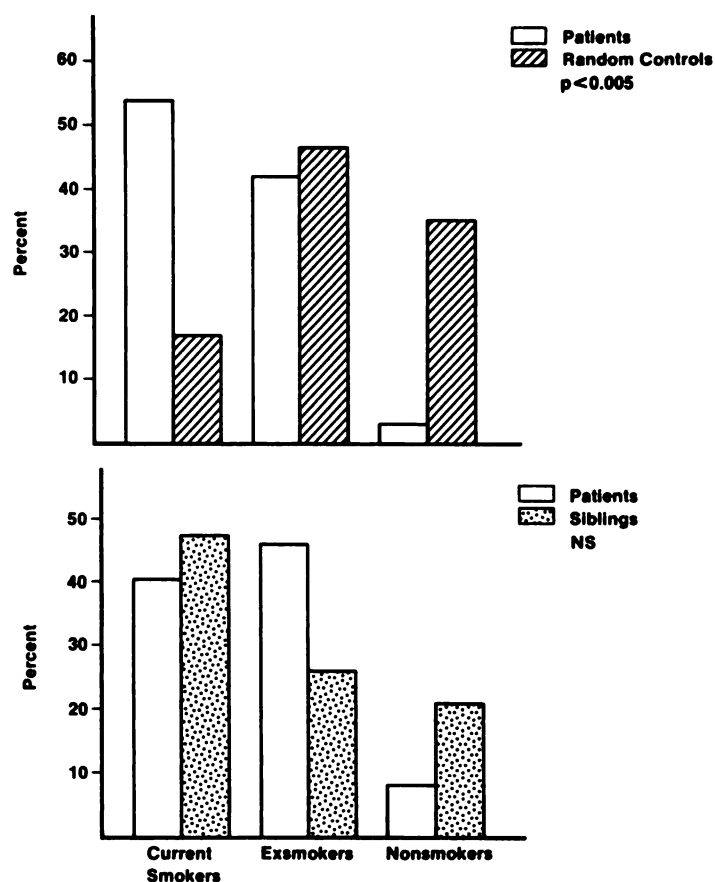


FIGURE 3. Distribution of current smokers, exsmokers and nonsmokers between patients with primary lung cancer and community control subjects (*upper panel*) and patients with primary lung cancer and siblings (*lower panel*).

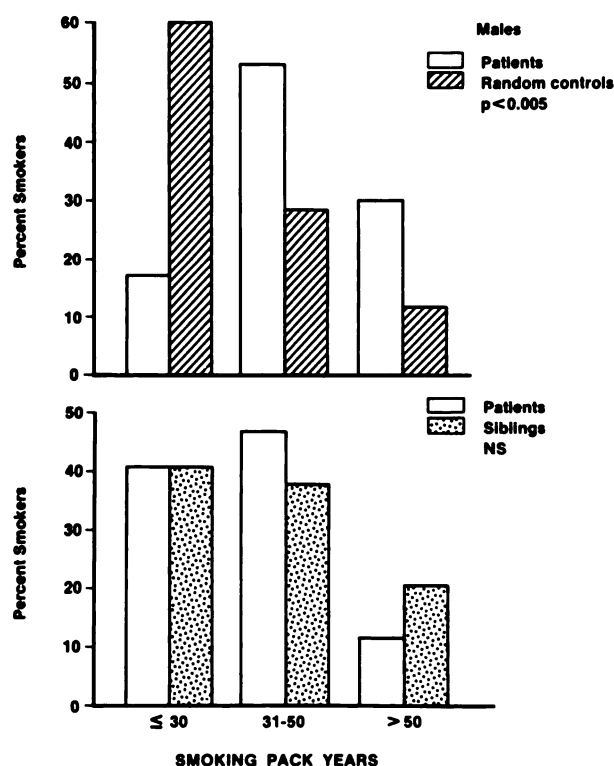


FIGURE 4. Distribution of pack-years of current and exsmokers.

Allergy skin test results are presented in Figures 1 and 2. Fewer patients (35.8 percent) than random community control subjects (58.4 percent) responded to $\geq$ one allergen ($p < .005$). However, the difference was nonsignificant when positive response to $\geq$ two allergens was examined (27.0 vs 37.2 percent, respectively). More subjects reacted to house dust mite and

to grain than to other substances. Similar proportions of those exposed to grains were skin-test positive: patients = .361 and community controls = .385.

There were significantly more current cigarette smokers among the patients (54.0 percent) than among the randomly selected control subjects (16.8 percent) ($p < .005$) (Fig 3). The distribution of pack-years was also significantly different between these two groups. An excess of patients over randomly selected control subjects also had a greater than a 30 pack-year history of smoking (Fig 4).

However, among male community control subjects there was no significant difference in the percentage of ever-cigarette-smokers among those who were not atopic (63.6 percent) and those who were (64.6 percent) as defined by allergy prick skin testing. In addition, the distribution of pack-years was similar, with 60 percent of both groups below 30 pack-years.

There was no significant difference in the demographic variables of age, education or residence in a city, town, village or on a farm between these patients with lung cancer and their same-sex sibling closest in age (Table 1). The distribution of occupations and their occupational exposures were also similar.

Comparison of the 38 sibling pairs revealed no significant difference in self-reported conditions, except for more allergies in the cancer-negative siblings ($p < .005$) (Fig 5). More patients reported morning cough ($p < .005$), and phlegm ($p < .005$) than did sibling control subjects, while more sibling control subjects than patients reported rhinitis ($p < .025$).

The allergen skin test results are presented in Figures 1 and 2. Significantly more sibling control

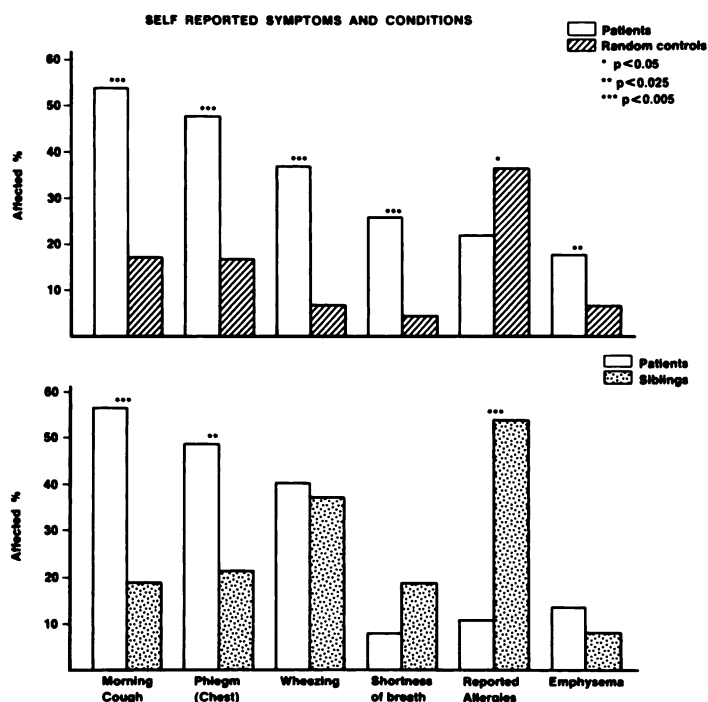


FIGURE 5. Upper panel shows self-reported symptoms and conditions of patients with primary lung cancer vs age- and sex-matched, randomly selected community control subjects. Lower panel shows data from patients with primary lung cancer and their same sex, closest-in-age sibling. Significant differences in distribution are indicated above appropriate bar graphs.

subjects reacted to $\geq$ one allergen ($p < .01$) and to $\geq$ two allergens than did the patients. There was, however, no significant difference in the distribution of current cigarette smokers, exsmokers and lifetime nonsmokers (Fig 3) and in the distribution of pack-years between the two groups (Fig 4).

DISCUSSION

A recent study¹ consisted of a retrospective investigation of a large number of cancer cases and control subjects to study the association of cancer and the report of previous diagnosis of asthma, hayfever, hives, and other allergy-related conditions. This and other studies²⁻¹⁰ have suggested an inverse association between such allergy-related diseases and cancer at several sites, including lung cancer. However, most of these studies have not been able to account for differences in smoking exposure which could influence the findings.

We have extended past studies by conducting an interview study of lung cancer patients and two sets of control subjects consisting of age-, sex-matched, randomly selected control subjects and nearest in age, same-sex sibling control subjects so as to reduce differences between cases and control subjects due to genetic factors, sex, and age.

We were able to perform a battery of allergy skin tests as well as obtain clinical histories of respiratory and allergy-related disorders and various occupational exposures. Our results indicate decreased evidence of atopy as manifested by the skin prick test in patients as compared to both the random control subjects and the sibling control subjects. However, the negative association is strongest between the patients and their sibling control subjects, in spite of a greater similarity of genetic and environmental factors. The only self-reported symptom or medical condition that both control groups report more frequently than the patients are allergies (random community controls $p < .05$, sibling control group $p < .005$). Control group siblings also report more rhinitis ($p < .025$).

There are several possible explanations for these data. First, atopy may lead to subject-directed reduction in exposure to one or more carcinogens (cigarette smoke). Secondly, cancer or its treatment may lead to suppression of objective manifestations of atopy. Finally, atopy may, either immunologically or non-immunologically, protect against the occurrence of malignancy. These possibilities will be discussed individually.

The first possibility, that atopic, self-selected reduction in smoking (or other carcinogen exposures), is particularly valid when considering bronchogenic carcinoma. The reduced incidence of bronchogenic carcinoma among asthmatic patients observed by Ford⁶ was felt to be due possibly to less smoking among the

asthmatic patients. Although it is unlikely that asymptomatic asthma or mild seasonal rhinitis (the vast majority of atopic subjects) would discourage smoking, subtle self-selection cannot be excluded. This may have been a factor in our study at least in the lung cancer vs community control groups, but did not appear to be a factor in the sibling control group, as smoking histories between patients and sibling control subjects were similar. This is also less likely to be a factor in the observations of others who have noted the negative association between atopy/allergy and other malignancies which are likely less related to cigarette smoking. In addition, we did not demonstrate differences in smoking habits or distribution of pack-years between atopic and non-atopic male community control subjects.

The second possibility, that carcinoma (or its treatment) could lead to altered objective expression of atopy, is also valid. Several mechanisms may be involved. Reduced immunologic expression could lead to lower IgE levels. This has been studied extensively and although somewhat conflicting results have been found,¹⁷ most authors agree that IgE levels in most cancer patients are normal.¹⁸⁻²⁰ Even if IgE levels were lower, the question of whether lower levels antedated or postdated the cancer cannot be answered. Treatment might also reduce immunologic parameters. Recently, Burtin et al²¹ have shown a reduction in end-organ (skin) sensitivity to histamine injections in cancer patients. These authors speculate that this might lead to reduction in other organ responses to released mediators of anaphylaxis. This could result in reduction in the size and number of positive skin test results and also possibly the magnitude of "current" atopic symptoms. However, unless memory is very short (a possibility in older cancer patients), remote symptoms of atopy should not be affected. We were careful to study our patients prior to any surgery, drug or radiation treatment, thus avoiding one possible confounder. Although it is possible that the skin responses were suppressed, either immunologically or nonimmunologically, by the cancer, the historic features of allergy are thought to be valid.

The final and most intriguing hypothesis is that atopy may protect against the development of cancer. Atopy is defined as the ability to develop IgE antibodies to commonly encountered environmental allergens under conditions of normal exposure.^{22,23} The precise mechanism underlying atopy is not certain. Although the end result is increased IgE levels, which could lead to increased local mucosal immunity, this is likely not the primary event.

In atopic subjects, sensitization occurs across mucosal membranes.²³ This leads to the possibility, perhaps even the likelihood, that the abnormality underlying atopy relates to the handling of allergen at the mucosal

level. It has been hypothesized that increased absorption of (potential) allergens leads to more efficient contact between the allergen and immunologic apparatus.²⁴ These mucosal barriers are generally single cell layers derived embryologically from the endoderm. In a previous study, we have demonstrated a strong negative correlation between endodermal malignancies (principally lung and gastrointestinal tract) and historic features of respiratory atopy.² Such a correlation was not seen for mesodermal malignancies (hemato-lympho-reticular and sarcomas) or for ectodermal malignancies (skin, breast). One hypothesis is that the mucosal surfaces of the atopic individual more efficiently handle allergens, leading to atopy, and carcinogens, leading to reduced cancer risk. A second hypothesis is that the secondary increase in IgE (and possibly other immune cells) might improve immunosurveillance and reduce cancer risk.

In summary, the current investigation provides support for the negative correlation between atopy and (endodermal) malignancy. We have extended previous studies by utilizing both objective data (skin tests) and subjective data (allergic history). It is unlikely that differences in smoking history caused these results and cancer treatment was not a factor. Changes in skin sensitivity caused by the cancer might have influenced the skin test results but not the history. The hypothesis that atopy either immunologically or non-immunologically protects against development of endodermal carcinoma, including cancer of the lung, warrants further, more fundamental investigation.

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