



Is the Risk of Lung Cancer Reduced among Eczema Patients?

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Persons with a history of eczema have been shown to have a reduced risk of lung cancer, but the evidence has been inconclusive because of the small size of previous studies and their limited ability to control for confounding by smoking. The objective of this study was to determine the role of eczema in relation to lung cancer while overcoming the limitations of previous investigations. Study subjects included 2,854 cases and 3,116 population and hospital controls recruited during 1998–2001 from 16 areas in the Czech Republic, Hungary, Poland, Romania, Russia, Slovakia, and the United Kingdom. Odds ratios were calculated for self-reported history of eczema via multivariate logistic regression modeling. The odds ratio for a history of eczema was 0.61 (95% confidence interval: 0.48, 0.76) after control for age, sex, study center, and cumulative tobacco smoking. There was no heterogeneity in the results by sex or age at onset of eczema. Subjects reporting use of medication for eczema had a lower odds ratio than subjects not reporting such use. This study provides further evidence for an inverse association between history of eczema and lung cancer risk, which is unlikely to be due to chance, bias, or confounding.

eczema; lung neoplasms

Abbreviations: CI, confidence interval; OR, odds ratio.

The association between cancer and history of allergic conditions has been investigated for more than 40 years. In particular, eczema is a suspected protective factor for several cancers and for all cancers combined (1–6), although this effect has not been observed in all studies (7, 8). Eczema is a pathologic reaction of the skin to endogenous

or exogenous agents. Primary lesions may include papules and vesicles that can coalesce to form patches and plaques. The prevalence of eczema increased in Europe during the second half of the 20th century, as did sensitization to pollen allergens (9). An inverse association of lung cancer with eczema and other atopic or allergic conditions such as

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asthma and hay fever has been observed in a limited number of studies (10–12); only one of them controlled for potential confounding by reduced tobacco smoking (10). Overall, available studies are limited in their ability to clarify the association, if any, between lung cancer and eczema.

Two hypotheses have been proposed to explain the relation between history of allergic conditions and cancer. According to the immunosurveillance hypothesis, allergies are associated with reduced cancer risk because of an enhanced ability of the immune system to eradicate malignant cells at an early stage of tumor development. An alternative theory suggests that immune-stimulating conditions, such as allergies, may actually increase the risk of cancer because chronic stimulation of cell growth provides more opportunity for random mutations in actively dividing stem cells and for proliferation of mutated clones (13).

Given the suggestive evidence for a reduced risk of lung cancer among eczema patients, we added this hypothesis to a large-scale epidemiologic study planned to investigate the role of environmental factors in lung carcinogenesis. We report here the results on the association between history of eczema and lung cancer risk with the specific goal of precisely estimating the magnitude of the effect, after careful control for potential confounders.

MATERIALS AND METHODS

A case-control study was conducted in 16 areas in seven countries: Brno, Olomouc, and Prague (Czech Republic); Budapest and the counties of Borsod-Abaúj-Zemplén, Heves, Szabolcs-Szatmár, and Jász-Nagykun-Szolnok (Hungary); Lodz and Warsaw (Poland); Bucharest (Romania); Moscow (Russia); Banská Bystrica, Bratislava, and Nitra (Slovakia); and Liverpool (United Kingdom). In each area, cases with newly diagnosed, histologically or cytologically confirmed primary lung cancer were recruited during 1998–2001 together with controls, who were frequency matched to cases by sex and age. Cases were recruited in hospitals that treated essentially all cases of lung cancers in each area, except in Moscow, where cases were recruited in two hospitals. Cases were identified through an active search of clinical and pathology departments and were selected within 3 months of diagnosis, so that only 13 cases died before interview. No next-of-kin interviews were performed. Cases and controls had to have lived in the study area for at least 1 year before diagnosis or interview. In all centers except Warsaw and Liverpool, hospital controls were recruited in general public hospitals serving the same area as the hospitals in which cases were identified. No single disease entity was attributed to more than 10 percent of the controls; patients admitted for cancer or tobacco-related diseases (e.g., chronic obstructive pulmonary disease, ischemic heart disease) were not considered eligible. Controls were randomly selected from eligible patients fulfilling the matching criteria. Population controls were selected from population registers in Warsaw and from the same general practitioner register as the cases in Liverpool.

Of 3,403 eligible cases, 549 (16.1 percent) were not included in the study: 27 had been discharged from the hospital before the interview, 53 were too ill to be interviewed,

TABLE 1. Selected characteristics of the study population recruited from 16 areas of seven countries to determine the role of eczema in relation to lung cancer, 1998–2001*

	Cases (N = 2,854)		Controls (N = 3,116)	
	No.	%	No.	%
Sex				
Men	2,198	77.0	2,304	73.9
Women	656	23.0	812	26.1
Age (years)				
<40	30	1.1	64	2.1
40–49	356	12.5	389	12.5
50–59	844	29.6	910	29.2
60–69	1,094	38.3	1,133	36.4
≥70	530	18.6	620	19.9
Country				
Czech Republic	302	10.6	494	15.9
Hungary	402	14.1	331	10.6
Poland	797	27.9	845	27.1
Romania	180	6.3	258	8.3
Russia	600	21.0	600	19.3
Slovakia	346	12.1	354	11.4
United Kingdom	227	8.0	234	7.5
Cumulative tobacco smoking (no. of pack-years)				
Never smoker	223	7.8	1,039	33.3
0.1–18.0	297	10.4	703	22.6
18.1–33.5	811	28.4	670	21.5
>33.5	1,516	53.1	690	22.1
Data missing	7		14	
Exposure to known or suspected occupational lung carcinogens				
Never	2,164	75.8	2,513	80.7
Ever	690	24.2	603	19.3

* Some percentages do not total 100 because of rounding.

13 had died before the interview, 449 refused to participate, and, for seven, information on history of eczema was missing. Of 3,670 eligible controls, 554 (15.1 percent) were not included in the study: 16 had been discharged from the hospital before the interview, 21 were too ill to be interviewed, two had died before the interview, 511 refused to participate, and, for four, information on age or history of eczema was missing. The study population included in the analysis therefore comprised 2,854 cases and 3,116 controls. Population controls represented 21.5 percent of the total series. Their distributions by sex, age, country, and tobacco smoking are reported in table 1. Men constituted three quarters of the study population; the age range of cases was 28–82 years and that of controls was 20–86 years. Poland and Russia provided the largest numbers of cases and controls. As expected, tobacco smoking was higher among cases than controls.

Interviewers were trained in a standardized manner at each study center to perform face-to-face interviews using standard questionnaires. Subjects were asked about their lifestyle habits, including diet, a detailed history of tobacco smoking, and occupation; specialized questionnaires were used for industries potentially entailing exposure to lung carcinogens. Probability, frequency, and level of exposure to 70 known or suspected lung carcinogens were assessed by teams of local experts on the basis of the information provided in the occupational questionnaires (14). In addition, cases and controls were asked about their history of nine diseases, including asthma and eczema, without requesting medical confirmation. For each medical condition, participants were asked about their age at first occurrence and their use of medications. The study was managed by a steering committee comprising the principal investigators from each country and the coordinators from the International Agency for Research on Cancer and the London School of Hygiene and Tropical Medicine. The coordinators periodically visited the study center to ensure adherence to the common protocol and organized regular meetings of the steering committee.

Statistical analyses were performed by using SAS software, version 8 (15). The primary analysis concerned ever report of eczema, and subjects with no history of eczema were included in the reference category. In secondary analyses, subjects with a history of eczema were divided according to age at onset (two categories with a cutpoint at 35 years, the median age of controls) and self-reported use of medications for eczema. Stratified analyses by age at diagnosis or interview (using the median for the whole study population), sex, asthma, exposure to known and suspected occupational lung carcinogens (16), and country were also conducted. Unconditional logistic regression models were fitted to the data to estimate the odds ratios of lung cancer and their 95 percent confidence intervals. All risk estimates were adjusted for attained age (nine categories), sex, study center, and cumulative tobacco smoking expressed as pack-years (nonsmokers and 10 levels of smoking based on the distribution among controls).

Exposure to occupational carcinogens was given particular importance as a potential confounder of the association between history of eczema and lung cancer risk; eczema patients might avoid contact with lung carcinogens, which are often also skin irritants, such as arsenic, cadmium and chromium compounds, coal-tar pitch, coal tar, soot, and ionizing radiation (17). We checked the correlation between history of eczema and exposure to these agents and other suspected lung carcinogens among controls, and we further adjusted risk estimates for exposure to occupational carcinogens as well as for diet and socioeconomic factors. Tests for interaction were computed for each stratified factor, and the heterogeneity *Q* test was used to assess the difference between categories of age at onset and of use of medication.

RESULTS

A history of eczema was reported by 156 cases (5.5 percent) and 275 controls (8.9 percent), resulting in a reduced odds ratio of lung cancer (table 2). The inverse association was observed in all countries except Romania (*p* of

TABLE 2. Odds ratios of lung cancer for history of eczema among persons recruited from 16 areas of seven countries, 1998–2001

Characteristic and history of eczema	Cases (no.)*	Controls (no.)*	OR†,‡	95% CI†
Whole population				
No	2,691	2,827	1.00	Reference
Yes	156	275	0.61	0.48, 0.76
Age (years)				
≤61				
No	1,358	1,433	1.00	Reference
Yes	92	137	0.70	0.51, 0.95
>61				
No	1,333	1,394	1.00	Reference
Yes	64	138	0.51	0.36, 0.72
Sex				
Women				
No	594	708	1.00	Reference
Yes	61	100	0.62	0.42, 0.92
Men				
No	2,097	2,119	1.00	Reference
Yes	95	175	0.60	0.45, 0.81
Asthma				
No				
No	2,553	2,696	1.00	Reference
Yes	140	247	0.63	0.49, 0.80
Yes				
No	135	131	1.00	Reference
Yes	16	27	0.45	0.19, 1.08
Cumulative tobacco smoking (no. of pack-years)				
Never smoker				
No	212	940	1.00	Reference
Yes	11	99	0.55	0.28, 1.08
0.1–18.0				
No	275	631	1.00	Reference
Yes	22	72	0.65	0.38, 1.11
18.1–33.5				
No	769	608	1.00	Reference
Yes	42	62	0.51	0.34, 0.79
>33.5				
No	1,435	648	1.00	Reference
Yes	81	42	0.80	0.54, 1.18
Exposure to known or suspected occupational carcinogens				
Never				
No	2,035	2,280	1.00	Reference
Yes	123	223	0.62	0.48, 0.80
Ever				
No	656	547	1.00	Reference
Yes	33	52	0.63	0.38, 1.05

* Numbers of cases and controls may not add to the total shown in table 1 because of missing data.

† OR, odds ratio; CI, confidence interval.

‡ Adjusted for age, sex, study center, and cumulative tobacco smoking.

interaction test = 0.11). Stratified analysis by age showed no difference in the protective effect between subjects older than age 61 years and younger ones (p of interaction test = 0.19). Similarly, stratification by sex did not reveal any difference in risk (p = 0.86). Analyses not adjusted for smoking yielded results similar to those shown in table 2 (odds ratio (OR) = 0.61, 95 percent confidence interval (CI): 0.50, 0.76). The results based on regression models including variables for smoking status (either ever/never or current/former/never smoker), number of cigarettes and other tobacco products smoked per day, and duration of smoking were not different from those reported in table 2. Inclusion in the regression model of a term for history of asthma resulted in an odds ratio of 0.61 (95 percent CI: 0.49, 0.77).

We found no association between history of eczema and exposure to occupational carcinogens, except for organic solvents (p = 0.05) and cadmium (p = 0.01) (to which people with eczema were exposed more frequently) and for ionizing radiation (p = 0.05) and meat and meat products (p = 0.03) (to which they were exposed less frequently). Adjustment for these exposures did not result in any modification of the risk estimates for history of eczema (OR = 0.61, 95 percent CI: 0.48, 0.77). Furthermore, the analysis including terms for educational level and consumption of fruits and vegetables resulted in odds ratios similar to those presented in the tables (OR for history of eczema = 0.63, 95 percent CI: 0.49, 0.79). Finally, adjustment for tobacco smoking using different approaches did not result in appreciable differences in the odds ratio for history of eczema (results not reported in detail).

The stratified analysis by asthma status showed no difference in the protective effect of eczema (p of interaction test = 0.57). However, the odds ratio for history of both eczema and asthma was lower than that for history of eczema alone.

The results of the analysis by age at onset of eczema and use of medications are shown in table 3. The odds ratio of lung cancer did not vary according to age at onset (p of heterogeneity test = 0.49) but was slightly lower for persons who reported having used medications for eczema than for others with eczema, although the difference was not statistically significant (p of heterogeneity test = 0.16). The analysis of combined effect of age at onset and use of medication was hampered by small numbers but did not suggest an interaction between these two factors.

An analysis stratified by main histologic type of lung cancer resulted in a lower odds ratio of squamous cell carcinoma (OR = 0.51, 95 percent CI: 0.36, 0.73; 1,134 cases) and of small cell carcinoma (OR = 0.54, 95 percent CI: 0.34, 0.85; 386 cases) than of adenocarcinoma (OR = 0.83, 95 percent CI: 0.58, 1.19; 587 cases; p for test of heterogeneity between the three types = 0.13).

DISCUSSION

In our study, self-reported history of eczema seemed to be associated with a reduced risk of lung cancer. This association did not appear to be modified by age at diagnosis of lung cancer, sex, or age at onset of eczema. The findings on use of medications may reflect a confounding effect by the

TABLE 3. Odds ratios of lung cancer by age at onset of eczema and use of medication among persons recruited from 16 areas of seven countries, 1998–2001

	Cases (no.)*	Controls (no.)*	OR†,‡	95% CI†
No history of eczema	2,691	2,827	1.00	Reference
Age (years) at onset of eczema				
≥35	71	134	0.56	0.41, 0.78
<35	70	115	0.66	0.47, 0.93
Use of medication for eczema				
Yes	99	196	0.55	0.41, 0.72
No	42	59	0.81	0.51, 1.28
Age (years) at onset and use of medication				
≥35 and yes	53	104	0.51	0.35, 0.75
≥35 and no	18	29	0.83	0.42, 1.63
<35 and yes	40	80	0.59	0.39, 0.92
<35 and no	19	19	1.01	0.48, 2.10

* Numbers of cases and controls might not add to the total shown in table 1 because of missing data.

† OR, odds ratio; CI, confidence interval.

‡ Adjusted for age, sex, study center, and cumulative tobacco smoking.

medication itself, but they might also reflect a dose-response relation, since those eczema patients who did not report having used medications may have had a milder form of eczema than other patients. The negative association was also present among persons not reporting a history of asthma. Patients reporting a history of both eczema and asthma had a particularly low odds ratio of lung cancer, which was imprecise, however, because of small numbers. The magnitude of the association we observed is similar to that reported in a previous study (10).

Chance is not a likely explanation for our results, which were highly statistically significant since they were based on large numbers of cases and controls. On the basis of the limited evidence available from previous studies, a negative association between lung cancer and allergic conditions, and eczema in particular, was one of the hypotheses that our study was designed to test.

Given the strong role of tobacco smoking in lung carcinogenesis, confounding by smoking (i.e., eczema patients smoking less than other people, possibly because of associated atopic conditions such as asthma) (18, 19) remains a plausible explanation for the observed association. Even after adjustment for tobacco smoking, residual confounding may remain undetected. We made a special effort to assess the possible confounding effect of tobacco smoking and of other potential confounders, but we found no evidence for such an effect.

In our study, as in retrospective studies in general, assessment of medical conditions may suffer from recall bias. However, the fact that eczema is an easily diagnosed

condition reduces the likelihood of such bias. Self-reporting has been used in large-scale studies, such as ISAAC and ECRHS, on the prevalence of allergic conditions (20, 21). Good specificity for self-reported hand eczema has been reported (96–99 percent) (22) as well as for self-diagnosis of “having a skin disease now” (100 percent) (23). A study on eczema itself found a specificity of 78 percent (24). Furthermore, the prevalence of eczema among controls in our study is comparable to (and in most cases is lower than) that reported in surveys of healthy European populations (20, 25, 26). In addition, bias might result from overrepresentation of eczema among controls. However, when we repeated the analysis after excluding 208 hospital controls with a current admission diagnosis of a disease potentially related to eczema, such as allergic reaction and dermatitis, the results were similar to those based on the whole study population.

An additional potential source of bias was inclusion of hospital controls and their identification in hospitals other than those in which cases were identified. Since the great majority of cases were identified in either cancer or pulmonary hospitals, it was necessary to select controls from other hospitals. We decided to select controls from general hospitals serving the same areas and to diversify the spectrum of admission diagnoses of controls to reduce the likelihood of selection bias. Moscow was the only study center in which cases represented only a fraction of all those originating in the study area: exclusion of this center, however, resulted in a minor change in the estimated odds ratio for history of eczema (OR = 0.63, 95 percent CI: 0.50, 0.81).

The strengths of this study lie in the large sample size, enabling us to estimate precisely the association between eczema and lung cancer; the detailed information on tobacco smoking and occupational exposures, enabling us to properly control for the main potential confounders; and the high response rate. In addition to the potential sources of bias discussed above, several limitations should be noted. The data available on history of eczema and other diseases were relatively crude, since the interview covered many other potential risks and protective factors for lung cancer. In particular, we lacked information on allergic and atopic diseases other than eczema and asthma and were not able to conduct analyses based on total number of allergic conditions, as previous studies did (e.g., Holly et al. (3), Severson et al. (4), Vena et al. (10)), severity of allergies (3), or exposure to allergens, including house dust, animals, plants, some foods, or mold (3, 13). More importantly, we were not able to distinguish between physician- and self-diagnosed eczema and, as discussed above, were unable to validate medical histories by reviewing medical records (22, 23). Although this limited our ability to investigate the specific nature of the associations found in more biologically meaningful ways (e.g., in relation to duration or severity of the allergy or in relation to specific immunologic characteristics of the host), it seems unlikely that this lack of detail would be manifested differentially between cases and controls in such a way as to produce a spurious inverse association of the magnitude observed.

Our results provide support for the hypothesis that altered immune function in relation to atopic and allergic condi-

tions, and to eczema in particular, plays a role in the etiology of lung cancer. The negative association we observed was relatively large and might be of significant clinical importance. Replication of our results is warranted in studies with a more detailed assessment of eczema and related conditions, coupled with a large sample size and good information on potential confounders.

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