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Lower Risk of Lung Cancer after Multiple Pneumonia Diagnoses

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Abstract

Background—Although pneumonia has been suggested as a risk factor for lung cancer, previous studies have not evaluated the influence of number of pneumonia diagnoses in relation to lung cancer risk.

Methods—The Environment And Genetics in Lung cancer Etiology (EAGLE) population-based study of 2,100 cases and 2,120 controls collected information on pneumonia more than one year before enrollment from 1,890 cases and 2,078 controls.

Results—After adjusting for study design variables, smoking, and chronic bronchitis, pneumonia was associated with decreased risk of lung cancer (odds ratio (OR), 0.79; 95% confidence interval (CI), 0.64–0.97), especially among individuals with ≥3 diagnoses versus none (OR, 0.35; 95% CI, 0.16–0.75). Adjustment for chronic bronchitis contributed to this inverse association. In comparison, pulmonary tuberculosis was not associated with lung cancer (OR, 0.96; 95% CI, 0.62–1.48).

Conclusions—The apparent protective effect of pneumonia among individuals with multiple pneumonia diagnoses may reflect an underlying difference in immune response and requires further investigation and confirmation.

Impact—Careful evaluation of number of pneumonia episodes may shed light on lung cancer etiology.

Keywords

pneumonia; epidemiology; lung cancer; multiple infections; tuberculosis

Introduction

Pulmonary infections have been proposed as risk factors for lung cancer (1). Respiratory tract infections may contribute to lung carcinogenesis by promoting airway remodeling (2) and causing inflammation, which can generate reactive oxygen or nitrogen species, increase cellular proliferation, upregulate antiapoptotic pathways, and stimulate angiogenesis (1). Both self-reported pneumonia and *Chlamydia pneumoniae* have been associated with increased lung cancer risk (1,3). While previous studies have evaluated any diagnosis of pneumonia and lung cancer, to our knowledge no previous study has analyzed the number of pneumonia diagnoses.

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The Environment And Genetics in Lung cancer Etiology population-based case control study (EAGLE) collected information on the number of self-reported pneumonia diagnoses, allowing detailed evaluation of the association with pneumonia. We also analyzed tuberculosis (TB).

Materials and Methods

As previously described (4), EAGLE enrolled 2,100 consecutive incident lung cancer cases from 13 hospitals in the Lombardy region of northern Italy, which accounted for approximately 80% of all lung cancer cases in the municipalities selected for the study, and 2,120 population-based controls randomly sampled from the Regional Health Service database and frequency matched to cases by age, sex, and area of residence. Of all eligible subjects, 86.6% of cases and 72.4% of controls agreed to participate and provided informed consent approved by the Institutional Review Boards of each participating hospital and university in Italy and the National Cancer Institute. All enrolled subjects were Caucasian.

Information on history of pneumonia and TB, including ages at diagnoses, was collected from cases and controls using a computer-assisted personal interview (CAPI). Data were collected for age at first, second, and third diagnosis of pneumonia, allowing evaluation of latency as the difference between study age (age at first diagnosis of lung cancer for cases or age at interview for controls) and age at first diagnosis. Seven cases and seven controls whose date of first pneumonia diagnosis was less than one year before study entry were excluded, leaving 2,094 cases and 2,113 controls. Of these, 1,890 (90.3%) cases and 2,078 (98.3%) controls provided data on pneumonia. These percentages are similar to the overall CAPI completion rates (cases, 92.6%; controls, 99.8%).

Lung cancer was confirmed from surgery, biopsy, or cytology samples in approximately 95% of cases, with confirmation through clinical history and imaging for the remainder (4). Main analyses included all primary lung cancer cases regardless of histological type, while histology-specific analyses included only adenocarcinoma, squamous cell carcinoma, large cell carcinoma, and small cell carcinoma, as defined by the WHO Histological Typing of Lung and Pleural Tumors (1999).

Odds ratios (ORs) and 95% confidence intervals (CIs) for associations with lung cancer were calculated through unconditional binary logistic regression for main analyses and polytomous logistic regression for analyses by histological type. All models included the design variables (study age, gender, and region) on which controls were frequency matched to cases. After backwards modeling to evaluate smoking (e.g., smoking intensity (average packs per day), time between last smoking quit attempt and study entry), demographic/socioeconomic variables (e.g., education, marital status), chronic bronchitis, emphysema, asthma, TB, family history of lung cancer in first degree relatives, and other factors as potential confounders, only the removal of chronic bronchitis changed the beta coefficient for pneumonia by more than 10%. However, in accord with several recent studies of adjustment for smoking (5–7), continuous pack-years and smoking intensity were included with history of chronic bronchitis in the final models. Additional smoking variables (time since quitting smoking, age at initiation of cigarette smoking, environmental tobacco smoke in childhood or adulthood (at work or home), and other tobacco smoking) had little impact on the ORs for pneumonia or TB and were not included in the final models. Similarly, additional adjustment for other self-reported previous lung diseases (emphysema, asthma, and TB in the pneumonia models) did not substantively change the results.

Effect modification by smoking and latency was evaluated using likelihood ratio tests (LRTs) for interaction. Differences in ORs for separate histological types were evaluated with the Wald test for homogeneity.

Results

The distribution of cases and controls is described in Table 1. Sixteen percent of cases (296/1,890) and 15% of controls (318/2,078) reported one or more pneumonia diagnoses (χ^2 P = 0.8). Three percent of both cases (61/1,881) and controls (62/2,070) reported TB (P = 0.3). The mean age at first diagnosis among cases and controls was 32.6 (median, 29; range, 0–78) for pneumonia and 24.9 (median, 22; range, 2–73) for TB. Over 90% of TB diagnoses were reported as occurring more than 20 years prior to study enrollment, compared to approximately 65% of initial pneumonia diagnoses. Pneumonia and TB were not associated: <1% of cases (*n* = 16) or controls (*n* = 17) had both.

The median time between diagnoses was 10 years (range, 1–71) among 87 people who reported age at first and second pneumonia diagnoses and 3 years (range, 1–33) among 23 people who reported age at second and third pneumonia diagnoses, suggesting separate episodes rather than unresolved infection. The median time between diagnoses was similar for cases and controls.

After adjustment, pneumonia reduced the risk of lung cancer (Table 2). This association did not vary by smoking status (LRT *P* = 0.6). The protective effect was strongest for patients with ≥3 diagnoses versus patients with no pneumonia diagnoses (OR, 0.35; 95% CI, 0.16–0.75). This pattern was similar for never, former, and current smokers, and the OR for pneumonia overall was similar if additionally adjusted for smoking status (OR: 0.78, 95% CI: 0.63– 0.96). Among subjects reporting pneumonia, the OR for ≥3 versus 1–2 diagnoses was 0.44 (95% CI, 0.20–0.97). Removal of chronic bronchitis from the model raised the fully adjusted OR for pneumonia from 0.79 (95% CI, 0.64–0.97) to 0.88 (95% CI, 0.72–1.08). While removing pack-years and smoking intensity had little effect (OR, 0.81; 95% CI, 0.67–0.98), removal of chronic bronchitis in addition to the smoking variables brought the OR to 0.99 (0.83–1.18). In contrast to pneumonia, TB was not associated with lung cancer (Table 2). Although risk of lung cancer increased somewhat across smoking status (LRT *P* = 0.02), numbers were quite small.

We evaluated the joint effects of pneumonia and chronic bronchitis (Table 3). The OR for pneumonia and lung cancer in individuals without chronic bronchitis was 0.83 (0.65–1.05), while chronic bronchitis was associated with increased risk of lung cancer regardless of pneumonia status. Even among individuals with chronic bronchitis, however, pneumonia had a protective effect (1.6/2.5=0.66; 95% CI, 0.43–1.04).

Pneumonia was not associated with attempting to quit smoking (OR, 1.05; 95% CI, 0.83–1.33) or number of quit attempts (*P*-trend = 1.0). The number of pneumonia diagnoses was similarly not associated with quitting smoking (data not shown). Among cases, neither pneumonia nor number of pneumonia diagnoses was associated with tumor stage (data not shown).

In addition to tumor stage, the associations for pneumonia and for TB did not vary by histology (Wald *P* = 0.8 and 0.7, respectively), although numbers were small for some histology categories. Histological results were similar when stratified by smoking status (data not shown). Likewise, associations of pneumonia and TB with lung cancer did not vary by quartiles of latency (LRT *P* = 0.7). ORs were inverse for individuals with ≥3 pneumonia diagnoses with no clear pattern by latency, while individuals with 1 or 2 diagnoses had inconsistent patterns tending to cluster around 1.0 (Table 4). Results were similar using latency calculated with the last known pneumonia diagnosis instead of the first.

Discussion

To our knowledge, this study is the first to evaluate the number of reported pneumonia diagnoses and lung cancer. Previous pneumonia was associated with decreased risk of lung

cancer, especially among individuals reporting ≥3 pneumonia diagnoses, whereas previous TB exhibited no association. Additional adjustment for smoking beyond pack-years and smoking intensity did not materially change these results, and there were no clear patterns by latency.

While previous studies generally have found positive associations between self-reported pneumonia and lung cancer (8–17), only one (15) controlled for chronic bronchitis. Since chronic bronchitis is clearly associated with increased risk of lung cancer (18) regardless of pneumonia status, chronic bronchitis may mask the true effect of pneumonia if chronic bronchitis is not taken into account. The etiologic factors for chronic bronchitis include smoking, genetics, and occupational and environmental exposures (19). Pneumonia is not thought to be important in etiology since studies such as Framingham establish that infectious exacerbations do not influence the underlying progression in decline of FEV1 (forced expiratory volume in 1 second) characteristic of chronic obstructive pulmonary disease (19). Since this evidence suggests that chronic bronchitis is not a key intermediate on the pathway from pneumonia to lung cancer, adjustment for chronic bronchitis was considered appropriate. Although longitudinal data are needed to clarify the relation between chronic bronchitis and pneumonia further, pneumonia reduced lung cancer risk even among subjects reporting no chronic bronchitis (OR, 0.83; 95% CI: 0.65–1.05). Adjusting for other lung diseases associated with lung cancer (18), such as emphysema, did not affect the association between pneumonia and lung cancer.

In our study, the inverse association appeared to be driven largely by the number of pneumonia diagnoses, although it is important to note that few individuals had ≥3 diagnoses. Previous studies have not addressed this issue. It is possible that having multiple bouts of pneumonia reflects some difference in immune function resulting in repeated pneumonia and an attenuated inflammatory response leading to slower progression to malignancy. Such an effect could be genetically mediated since family history of pneumonia also appears to decrease the risk of lung cancer, especially among older individuals (20). Alternatively, antibiotic treatment for pneumonia may eliminate infectious agents reported to increase lung cancer risk, such as *Chlamydia pneumoniae* (3). Thus, repeated treatment courses for multiple bouts of pneumonia might decrease the risk of lung cancer. Although people with pneumonia might, in theory, be more likely to reduce or quit smoking or avoid other environmental risk factors for lung cancer, adjusting for smoking and other factors only strengthened the inverse association in our study. Finally, the “immunesurveillance hypothesis” proposed for asthma may be relevant in this case: multiple bouts of pneumonia may stimulate the immune system such that it is better able to detect and destroy cancer cells (21). While we are unsure why we see inverse associations, our findings warrant further investigation in other studies with data on multiple pneumonia diagnoses.

TB and lung cancer exhibited no association in our data. Reported associations between TB and lung cancer have been inconsistent (8–12,15–17,22–25) and often weaker with longer latency (9,16,22,25). In our study, the median age at TB diagnosis was 22, and diagnosis occurred more than 20 years prior to interview in over 90% of subjects. Thus, it may not be surprising that we found no association since the association between TB and lung cancer weakens with longer latency (22). Individuals diagnosed with TB at a young age may tend to avoid risk factors like smoking, thus reducing their risk for lung cancer.

These results must be interpreted with caution given the potential for misclassification through self-report and the small number of subjects with ≥3 pneumonia diagnoses. Although recall bias is of concern as in all case-control studies, the same persons did not report both pneumonia and TB, suggesting that there was not consistent differential error in reporting incases or controls. While it is theoretically possible that lung cancer may be diagnosed earlier in exposed individuals due to increased medical investigations like chest X-rays, pneumonia was not

associated with tumor stage. In addition, such surveillance bias would increase the OR and thus cannot account for the inverse association we observed between pneumonia and lung cancer, but could lead to a bias towards a weaker estimate of effect.

EAGLE is an excellent setting in which to evaluate pneumonia and lung cancer given its large size, population-based design, detailed questionnaires including number of pneumonia diagnoses, and high participation rate. Interviewers were centrally trained to ensure accurate and complete data collection. Data collection and transfer were further protected through extensive quality control procedures (4).

In one of the largest studies of previous pneumonia and lung cancer to date and the first to our knowledge to report on number of pneumonia diagnoses, we found a novel inverse association between pneumonia and lung cancer. Given that this result was largely limited to people with ≥3 pneumonia diagnoses, we speculate that some immune perturbation or effect of treatment accounts for the decreased risk of lung cancer in these individuals. Future studies focused on these individuals, perhaps with specific attention to genetic polymorphisms, may help elucidate the underlying mechanisms involved in lung carcinogenesis.

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Table 1

Descriptive characteristics of cases and controls providing data on pneumonia at least one year prior to entry into the Environment And Genetics in Lung cancer Etiology (EAGLE) case-control study.

Characteristic	Cases (N = 1890)	Controls (N = 2078)	P-value
Median age (range)	67 (35–80)	66 (35–80)	0.02
% male	79.2	76.4	0.04
Study area N (%)			0.9
Brescia	238 (12.6)	242 (11.6)	
Milano	1242 (65.7)	1417 (68.2)	
Monza	129 (6.8)	116 (5.6)	
Pavia	125 (6.6)	126 (6.1)	
Varese	156 (8.3)	177 (8.5)	
% ever smokers	93.0	67.8	<0.0001
Median smoking intensity (average packs/day)	1.0	0.75	<0.0001
Median duration of smoking (years)	44	33	<0.0001
Education, N (%)*			<0.0001
None	107 (5.7)	90 (4.3)	
Elementary	734 (38.9)	557 (26.8)	
Middle school	541 (28.6)	601 (28.9)	
High school	411 (21.8)	568 (27.3)	
University	96 (5.1)	262 (12.6)	
% Married/cohabitating	77.0	82.8	<0.0001

* Does not sum to total due to missing values

Table 2

Odds ratios (OR) and 95% confidence intervals (CI) for associations of lung cancer with pneumonia and tuberculosis diagnosed at least one year prior to entry into the Environment And Genetics in Lung cancer Etiology (EAGLE) case-control study, both overall and stratified by smoking status.

	Overall			Smoking Status								
				Never			Former			Current		
	Cases *n=1846* (%)	Controls *n=2054* (%)	OR (95% CI)*	Cases *n=131* (%)	Controls *n=666* (%)	OR (95% CI)*	Cases *n=791* (%)	Controls *n=879* (%)	OR (95% CI)*	Cases *n=924* (%)	Controls *n=509* (%)	OR (95% CI)*
Pneumonia†												
No	1555 (84.2)	1746 (85.0)	1	118 (90.1)	586 (88.0)	1	647 (81.8)	727 (82.7)	1	790 (85.5)	433 (85.1)	1
Yes	291 (15.8)	308 (15.0)	0.79 (0.64–0.97)	13 (9.9)	80 (12.0)	0.72 (0.37–1.41)	144 (18.2)	152 (17.3)	0.83 (0.62–1.12)	134 (14.5)	76 (14.9)	0.75 (0.54–1.06)
1 diagnosis	240 (13.0)	253 (12.3)	0.81 (0.65–1.02)	11 (8.4)	61 (9.2)	0.89 (0.44–1.83)	113 (14.3)	128 (14.6)	0.83 (0.60–1.12)	116 (12.6)	64 (12.6)	0.78 (0.54–1.12)
2 diagnoses	35 (1.9)	33 (1.6)	0.97 (0.55–1.71)	2 (1.5)	12 (1.8)	0.59 (0.12–2.95)	22 (2.8)	14 (1.6)	1.25 (0.58–2.71)	11 (1.2)	7 (1.4)	0.78 (0.28–2.20)
≥3 diagnoses	16 (0.9)	22 (1.1)	0.35 (0.16–0.75)	0 (0.0)	7 (1.1)	0	9 (1.1)	10 (1.1)	0.49 (0.17–1.42)	7 (0.8)	5 (1.0)	0.38 (0.22–1.30)
P -trend			0.008			0.1			0.2			0.06
Tuberculosis†												
No	1777 (96.7)	1985 (97.0)	1	128 (98.5)	643 (96.8)	1	764 (96.8)	843 (96.2)	1	885 (96.4)	499 (98.6)	1
Yes	60 (3.3)	61 (3.0)	0.96 (0.62–1.48)	2 (1.5)	21 (3.2)	0.40 (0.09–1.89)	25 (3.2)	33 (3.8)	0.87 (0.48–1.58)	33 (3.6)	7 (1.4)	1.73 (0.72–4.14)

*Adjusted for study age, sex, region, and chronic bronchitis for never smokers and also pack-years and smoking intensity (average packs per day) for smokers and overall

†Overall number does not sum to total due to subjects missing data on other variables included in the multivariate model

Table 3

Distribution of pneumonia among individuals with and without history of chronic bronchitis in the Environment And Genetics in Lung cancer Etiology (EAGLE) case-control study and odds ratios (OR) and 95% confidence intervals (CI) for the risk of lung cancer among individuals with pneumonia only, chronic bronchitis only, or both pneumonia and chronic bronchitis compared to individuals without chronic bronchitis (referent)

	History of chronic bronchitis	
History of pneumonia*	**No**	**Yes**
No		
n cases	1266	289
n controls	1659	87
OR (95% CI)†	Referent	2.45 (1.85–3.25)
Yes		
n cases	172	119
n controls	253	55
OR (95% CI)†	0.83 (0.65–1.05)	1.63 (1.12–2.36)

*Numbers do not sum to total due to subjects missing data on other variables included in the multivariate model

†OR = odds ratio, CI = confidence interval. Adjusted for study age, gender, region, pack-years, and smoking intensity (average packs per day)

Table 4

Odds ratios* (OR) and 95% confidence intervals (CI) for the association of lung cancer with pneumonia latency (time from first or last known pneumonia diagnosis to lung cancer or interview) using tertiles in controls (based on time from first pneumonia diagnosis), stratified by number of pneumonia diagnoses.

Pneumonia latency		Based on first pneumonia diagnosis			Based on last known pneumonia diagnosis		
***n* diagnoses**	**Tertile (years)**	***n* cases†**	***n* controls†**	**OR (95% CI)***	***n* cases†**	***n* controls†**	**OR (95% CI)***
0	Not applicable	1555	1746	1.0	1555	1746	1.0
1	1st (1-<23)	111	84	0.99 (0.70–1.40)	111	84	0.99 (0.70–1.40)
1	2nd (23-<53)	51	76	0.64 (0.41–0.98)	51	76	0.64 (0.41–0.98)
1	3rd (≥53)	64	72	0.87 (0.59–1.30)	64	72	0.87 (0.59–1.30)
2	1st (1-<23)	5	3	1.83 (0.35–9.55)	22	14	1.50 (0.69–3.24)
2	2nd (23-<53)	13	9	1.63 (0.63–4.23)	8	11	0.72 (0.25–2.09)
2	3rd (≥53)	14	16	0.92 (0.41–2.07)	4	4	1.15 (0.25–5.24)
≥3	1st (1-<23)	2	3	0.43 (0.06–3.31)	9	8	0.62 (0.21–1.83)
≥3	2nd (23-<53)	5	7	0.33 (0.09–1.23)	2	6	0.07 (0.01–0.39)
≥3	3rd (≥53)	7	6	0.61 (0.15–2.39)	3	5	0.32 (0.05–2.00)

*Referent is no report of pneumonia. Adjusted for study age, gender, region, pack-years, smoking intensity (average packs per day), and chronic bronchitis

†Numbers do not sum to total due to subjects missing data on other variables included in the multivariate model or subjects who answered “Don’t know” for one or more age at diagnosis of pneumonia variable