Chronic Obstructive Pulmonary Disease and Altered Risk of Lung Cancer in a Population-Based Case-Control Study

Jill Koshiol1*, Melissa Rotunno1, Dario Consonni2, Angela Cecilia Pesatori2, Sara De Matteis2, Alisa M. Goldstein1, Anil K. Chaturvedi1, Sholom Wacholder1, Maria Teresa Landi1, Jay H. Lubin1, Neil E. Caporaso1

1 Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, Maryland, United States of America, 2 EPOCA Research Center, Department of Occupational and Environmental Health, Università degli Studi di Milano, and Epidemiology Unit, Fondazione IRCCS Ospedale Maggiore Policlinico, Mangiagalli e Regina Elena, Milan, Italy

Abstract

Background: Chronic obstructive pulmonary disease (COPD) has been consistently associated with increased risk of lung cancer. However, previous studies have had limited ability to determine whether the association is due to smoking.

Methodology/Principal Findings: The Environment And Genetics in Lung cancer Etiology (EAGLE) population-based case-control study recruited 2100 cases and 2120 controls, of whom 1934 cases and 2108 controls reported about diagnosis of chronic bronchitis, emphysema, COPD (chronic bronchitis and/or emphysema), or asthma more than 1 year before enrollment. We estimated odds ratios (OR) and 95% confidence intervals (CI) using logistic regression. After adjustment for smoking, other previous lung diseases, and study design variables, lung cancer risk was elevated among individuals with a history of chronic bronchitis (OR = 2.0, 95% CI = 1.5–2.5), emphysema (OR = 1.9, 95% CI = 1.4–2.8), or COPD (OR = 2.5, 95% CI = 2.0–3.1). Among current smokers, association between chronic bronchitis and lung cancer was strongest among lighter smokers. Asthma was associated with a decreased risk of lung cancer in males (OR = 0.48, 95% CI = 0.30–0.78).

Conclusions/Significance: These results suggest that the associations of personal history of chronic bronchitis, emphysema, and COPD with increased risk of lung cancer are not entirely due to smoking. Inflammatory processes may both contribute to COPD and be important for lung carcinogenesis.

Introduction

Every year, over 1 million people die from lung cancer worldwide [1]. Although cigarette smoking is the primary etiologic agent in 85–90% of all lung cancers [2], only 10–15% of active smokers develop lung cancer [3]. In addition, lung cancer is the seventh most common cause of cancer death worldwide in never smokers [4]. While risk factors such as family history of lung cancer, occupational carcinogens, and radon account for some increased risk, the etiology of lung cancer in this population remains poorly understood [4]. Associations between nicotine receptors and lung cancer from genome-wide association studies [5–7] only account for a small component of the increased risk, suggesting that additional factors must be involved in lung carcinogenesis.

Chronic obstructive pulmonary disease (COPD) has been suggested as a risk factor for lung cancer. COPD can be exacerbated by pulmonary infections [8,9] that cause inflammation, which contributes to lung carcinogenesis [10], and carcinogenesis in general [11], by generating reactive oxygen or nitrogen species, increasing cellular proliferation, upregulating antiapoptotic pathways, and stimulating angiogenesis [10]. Infections may also promote airway remodeling that could enhance carcinogenesis [12]. Although COPD is strongly and consistently associated with lung cancer [13–16], the degree to which the association between COPD and lung cancer is due to smoking or other factors remains unclear [3]. Few studies have had appropriate data and sufficient cases to evaluate COPD and lung cancer by histology and time since diagnosis of previous COPD.

The Environment And Genetics in Lung Cancer Etiology population-based case-control study (EAGLE) was specifically designed to evaluate comprehensively a variety of risk factors for lung cancer. With over 2000 cases, EAGLE allows evaluation of the association of COPD and lung cancer by smoking status, histology, gender, and time since COPD diagnosis.

* E-mail: koshiolj@mail.nih.gov

Competing Interests: The authors have declared that no competing interests exist.
Materials and Methods

The EAGLE study has previously been described [17]. In brief, EAGLE is a large population-based study of 2100 consecutive incident lung cancer cases and 2120 controls from the Lombardy region of northern Italy. Cases were enrolled from 13 hospitals in 216 municipalities including 3 large cities (Milan, Monza, Brescia, Pavia, and Varese). Healthy controls were randomly sampled from the Regional Health Service database and frequency matched to cases by age, sex, and area of residence. The participation rates (number of subjects who agreed to participate/eligible subjects) were 86.6% for cases and 72.4% for controls. Each participant provided written informed consent. The study was approved by the Institutional Review Board (IRB) of each participating hospital and university in Italy and by the National Cancer Institute, Bethesda, MD.

We defined COPD as reporting a diagnosis of chronic bronchitis and/or emphysema. We chose not to include asthma in the definition of COPD since asthma is not strongly associated with smoking and often develops in childhood [18,19], whereas chronic bronchitis and emphysema are strongly associated with smoking, occur more commonly with increasing age, and often occur together [20–22]. We included asthma separately since historically it has been considered a component of COPD [23].

Participants were asked (in Italian) through a computer-assisted personal interview (CAPI) “whether a doctor ever told you more than one year ago that you had any of these conditions: chronic bronchitis, emphysema, asthma” and “How old were you when this condition was first diagnosed?” We evaluated chronic bronchitis and emphysema both independently and jointly. We calculated latency for each condition as the difference between study age (age at first diagnosis of lung cancer or interview) and age at first diagnosis of previous lung disease. Ten cases and four controls who provided a date of previous chronic bronchitis, emphysema, or asthma less than one year before study entry were excluded, leaving 2091 cases and 2116 controls. Of these, 1934 (92.5%) cases and 2108 (99.6%) controls provided data on chronic bronchitis, emphysema, or asthma. These percentages are similar to the overall CAPI completion rates for cases (92.6%) and controls (99.8%).

Lung cancer was diagnosed according to standard clinical criteria with pathologic confirmation from surgery, biopsy, or cytology samples in approximately 95% of cases. The remaining cases were confirmed through clinical history and imaging [17]. Main analyses included all primary lung cancer cases regardless of histological type. Histology-specific analyses were restricted to adenocarcinoma, squamous cell carcinoma, large cell carcinoma, or small cell carcinoma. Tumor histology was defined using the WHO Histological Typing of Lung and Pleural Tumors (1999).

We used unconditional binary logistic regression to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for the association of chronic bronchitis, emphysema, COPD, and asthma with lung cancer and polycystic logistic regression to calculate ORs and 95% CIs by histological type. All models included the design variables (study age, gender, and region). Potential confounders, including smoking (e.g., smoking intensity (average packs per day), time since last smoking quit attempt and entry into EAGLE), demographic/socioeconomic variables (e.g., education, marital status), and other factors, were evaluated through backwards modeling using chronic bronchitis as the main exposure. Since the removal of continuous pack-years, emphysema, and pneumonia changed the beta coefficient for chronic bronchitis by more than 10%, they were retained in the adjusted models. In accord with several recent studies [24–26], we selected pack-years and smoking intensity to adjust for smoking exposure; however, models using other closely related smoking metrics (smoking duration; time since quitting smoking; age at initiation of cigarette smoking; environmental tobacco smoke in childhood, adulthood at work, or adulthood at home; and other tobacco smoking) produced almost identical results. Chronic bronchitis changed the beta coefficient for emphysema by more than 10% and thus was included in multivariate models where chronic bronchitis was not the main effect or a component of the main effect (i.e., COPD).

Smoking, gender, and latency were evaluated as effect-measure modifiers using likelihood ratio tests (LRTs) for interaction on the multiplicative scale adjusted as described above. Differences in ORs for separate histological types were evaluated with the Wald test for homogeneity.

Results

Compared to controls, cases tended to be less educated, less likely to be married or cohabitating, and more likely to be current smokers [Table 1]. Among smokers, the mean smoking intensity (average packs per day) was 1.1 (standard deviation (SD) = 0.5) among cases and 0.8 (SD = 0.5) among controls, and the mean pack-years was 48.6 (SD = 27.9) among cases and 27.3 (SD = 22.1) among controls. Among cases, the mean age at diagnosis of chronic bronchitis was 45.0 years (median = 48, range = 0–78) in cases and 56.4 years (median = 61, range = 3–77) in controls (t-test for difference in group means p-value <0.001), of emphysema was 54.2 years (median 57, range 6–77) in cases and 56.3 years (median 58, range = 18–78) in controls (t-test p-value = 0.3), of COPD was 46.4 years (median = 50, range = 0–78) in cases and 56.4 years (median = 60, range 3–78) in controls (t-test p-value <0.001), and of asthma was 39.1 years (median = 44, range = 0–75) in cases and 41.6 years (median = 49, range = 1–77) in controls (t-test p-value = 0.5).

After adjustment for smoking and other factors, chronic bronchitis, emphysema, and COPD were associated with an approximately two-fold increased risk of lung cancer [Table 2]. Results were similar when restricted to individuals diagnosed with chronic bronchitis, emphysema, or COPD at or above age 18 (data not shown). Evaluating chronic bronchitis and emphysema as a combined variable, the OR for having both chronic bronchitis and emphysema (2.5, 95% CI 1.6–4.0) was similar to the ORs for having chronic bronchitis only (2.3, 95% CI 1.8–3.0) or emphysema only (2.9, 95% CI 1.8–4.6). Given that the OR for having both chronic bronchitis and emphysema was no stronger than having chronic bronchitis or emphysema separately, chronic bronchitis and emphysema were maintained as separate variables. In a subset of cases with spirometry data available, self-report-based COPD was strongly associated spirometry-based COPD (OR = 3.0, 95% CI = 2.1–4.3).

Although gender did not modify the association of lung cancer with chronic bronchitis, emphysema, or COPD (LRT p-values = 0.4, 0.3, 0.6, respectively), the OR for asthma among males was 0.48 (95% CI = 0.30–0.78) and among females was 1.1 (95% CI = 0.57–2.3) [LRT p-value for interaction = 0.03]. Among men, even the minimally adjusted OR suggested an inverse association, which was substantially strengthened after accounting for chronic bronchitis and emphysema, both of which increased the risk of lung cancer [Table 2]. Among women there was no association regardless of adjustment. Since only 48 women (23 cases) reported asthma diagnosis, additional analyses focused on men with more limited analyses in women.

The ORs for chronic bronchitis and asthma did not vary by smoking status [Table 3]. We observed an increased risk with
emphysema only among smokers, although only two never-smoking cases had emphysema, limiting power to detect differences by smoking status (LRT p-value = 0.3). Similarly, the strongest effect of COPD was seen in smokers, although the LRT p-value was 0.4. Restricted to current smokers, the strength of the association between chronic bronchitis and lung cancer decreased with increasing pack-years, smoking intensity, and smoking duration [Table 4] (LRT p-values for continuous pack-years and smoking intensity <0.001, smoking duration 0.02). The trends for COPD were similar to those for chronic bronchitis. Emphysema and asthma in males showed no clear pattern by pack-years, smoking intensity, and smoking duration. There were too few women with asthma for extended analyses by smoking status. Risk of lung cancer increased with time since diagnosis of chronic bronchitis (LRT p-value = 0.002) and COPD (LRT p-value = 0.007) but did not consistently increase or decrease with time since diagnosis of emphysema (LRT p-value = 0.2) or asthma among males (LRT p-value = 0.9) [Table 5]. The asthma in males was consistently associated with a decreased risk of lung cancer for asthma diagnosed more than five years prior, however. Among women, the OR for asthma diagnosed 1–5 years prior to lung cancer or enrollment was 0.50 (95% CI = 0.09–2.9) and for asthma diagnosed >5 years prior was 1.7 (95% CI = 0.75–4.0). LRT p-value = 0.4). The distribution of ever/never smoking, time since last quit smoking, and family history of lung cancer varied little by latency (data not shown). Although latency and age at diagnosis are highly correlated, we also evaluated the association of age at diagnosis of chronic bronchitis or COPD with risk of lung cancer since the mean age at diagnosis of chronic bronchitis and COPD differed for cases and controls. The age at diagnosis results mirrored the latency results. Restricting to subjects with known age at diagnosis, later age at diagnosis (and thus likely shorter latency) was associated with decreased risk of lung cancer for both chronic bronchitis (OR = 0.95, 95% CI = 0.93–0.97) and COPD (OR = 0.95, 95% CI = 0.93–0.97).

The associations of lung cancer with chronic bronchitis, emphysema, COPD, asthma in men, and asthma in women did not vary by histology (Wald p-value = 0.4, 0.4, 0.7, 0.6, 0.7, respectively), although numbers were small for some histology categories. We also stratified by high and low pack-years for adenocarcinoma separately because this histologic subgroup exhibits demographic, smoking-related [4, 28], and molecular [29, 30] differences compared with other histologies. Among ever smokers, the OR for chronic bronchitis was 1.8 (95% CI = 0.91–3.7) for adenocarcinoma and ≤24 pack-years, 1.7 (95% CI = 1.2–2.4) for adenocarcinoma and >24 pack-years, 3.7 (95% CI = 3.8–7.6) for other histologies (squamous cell, large cell, and small cell carcinoma) and ≤24 pack-years, 1.6 (95% CI = 1.1–2.2) for other histologies and >24 pack-years (LRT p-value = 0.02). The associations of emphysema, COPD, and asthma and risk of adenocarcinoma and other histologies varied little by high or low pack-years (LRT p-values = 0.4, 0.2, and 0.2, respectively).

### Discussion

In this large study of chronic obstructive pulmonary disease (COPD) and lung cancer, we found that history of chronic bronchitis, emphysema, and COPD were associated with increased risk of lung cancer. The risk in patients with both chronic bronchitis and emphysema was similar to that in patients with only chronic bronchitis or emphysema. Previous asthma was associated with decreased risk of lung cancer in males. Additional adjustment for smoking beyond pack-years and smoking intensity did not materially change these results. While there is strong and compelling evidence for associations between COPD and lung cancer [14–16, 31], some have argued that this association may be largely due to smoking, even after adjustment [32]. However, several lines of evidence suggest that the association between COPD and lung cancer may not be entirely due to smoking. Family history of chronic bronchitis and emphysema are associated with increased risk of lung cancer [33]. In addition, COPD is associated with lung cancer in never-smokers [31]. A recent study estimated that COPD accounts for 10% of lung cancer cases among never smokers and 12% among

---

**Table 1. Distribution of cases and controls in the Environment And Genetics in Lung cancer Etiology study who provided data on chronic bronchitis, emphysema, or asthma diagnosed at least one year prior to study entry.**

| Characteristic | Sub-category | Cases | N  | %  | Controls | N  | %  |
|---------------|--------------|-------|----|----|----------|----|----|
| Study age     | <60          | 420   | 21.7 | 543 | 25.8     |     |    |
|               | 60–<65       | 339   | 17.5 | 370 | 17.6     |     |    |
|               | 65–<70       | 429   | 22.2 | 486 | 23.1     |     |    |
|               | > =70        | 746   | 38.6 | 709 | 33.6     |     |    |
| Gender        | Male         | 1528  | 79.0 | 1610| 76.4     |     |    |
|               | Female       | 406   | 21.0 | 498 | 23.6     |     |    |
| Education*    | None         | 112   | 5.8  | 90  | 4.3      |     |    |
|               | Elementary   | 748   | 38.7 | 570 | 27.0     |     |    |
|               | Middle school| 554   | 28.7 | 612 | 29.0     |     |    |
|               | High school  | 418   | 21.6 | 574 | 27.2     |     |    |
|               | University   | 101   | 5.2  | 262 | 12.4     |     |    |
| Marital status| Married/cohabitating | 1491 | 77.1 | 1741| 82.6     |     |    |
|               | Not married/cohabiting | 443  | 22.9 | 367 | 17.4     |     |    |
| Smoking status* | Never       | 133   | 6.9  | 678 | 32.2     |     |    |
|               | Former       | 833   | 43.1 | 905 | 43.0     |     |    |
|               | Current      | 968   | 50.1 | 524 | 24.9     |     |    |
| Chronic bronchitis* | No           | 1466  | 77.7 | 1943| 93.1     |     |    |
|               | Yes          | 421   | 22.3 | 144 | 6.9      |     |    |
| Emphysema*    | No           | 1699  | 89.3 | 2038| 97.0     |     |    |
|               | Yes          | 203   | 10.7 | 62  | 3.0      |     |    |
| COPD*         | No           | 1372  | 72.9 | 1908| 91.6     |     |    |
|               | Yes          | 509   | 27.1 | 174 | 8.4      |     |    |
| Asthma*       | No           | 1836  | 95.9 | 2005| 95.3     |     |    |
|               | Yes          | 78    | 4.1  | 99  | 4.7      |     |    |

*Does not sum to total due to missing values.

1COPD = chronic obstructive pulmonary disease (chronic bronchitis and/or emphysema).

doi:10.1371/journal.pone.0007380.t001
heavy smokers [34]. We found that even restricted to adenocarcinoma, which is more common among non-smokers, particularly women [4], COPD remained strongly associated with lung cancer. In addition, the association between chronic bronchitis and lung cancer was stronger among smokers with lower pack-years, smoking intensity, and smoking duration. The stronger association

Table 2. Associations of lung cancer with lung disease diagnosed at least one year prior in the Environment And Genetics in Lung cancer Etiology case-control study.

| Lung disease | Sub-category | Minimally Adjusted OR (95% CI)* | Fully Adjusted OR (95% CI)† |
|--------------|--------------|---------------------------------|-----------------------------|
| Chronic bronchitis | No | 1.0 | 1.0 |
| | Yes | 3.8 (3.1–4.7) | 2.0 (1.6–2.5) |
| Emphysema | No | 1.0 | 1.0 |
| | Yes | 3.8 (2.8–5.1) | 1.9 (1.4–2.7) |
| COPD‡ | No | 1.0 | 1.0 |
| | Yes | 4.1 (3.4–4.9) | 2.5 (2.0–3.1) |
| Asthma in males | No | 1.0 | 1.0 |
| | Yes | 0.77 (0.54–1.1) | 0.48 (0.30–0.78) |
| Asthma in females | No | 1.0 | 1.0 |
| | Yes | 0.11 (0.64–2.0) | 1.1 (0.57–2.3) |

*OR = odds ratio, CI = confidence interval. Adjusted for study age, sex, and region.
†OR = odds ratio, CI = confidence interval. Adjusted for study age, sex, region, pack-years, amount of cigarette smoking (average packs/day), bronchitis (unless main effect or COPD), emphysema (unless main effect or COPD), and pneumonia.
‡COPD = chronic obstructive pulmonary disease (chronic bronchitis and/or emphysema).

Table 3. Associations of lung cancer with lung disease diagnosed at least one year prior and lung cancer in the Environment And Genetics in Lung cancer Etiology case-control study, stratified by smoking status.

| Lung Disease | Sub-category | Never | Former | Current | LRT‡ p-value |
|--------------|--------------|-------|--------|---------|-------------|
| Chronic bronchitis | Cases, N yes/total (%) | 7/131 (5.3) | 185/813 (22.8) | 229/943 (24.3) | 0.6 |
| | Controls, N yes/total (%) | 20/673 (3.0) | 70/895 (7.8) | 54/519 (10.4) | |
| | OR (95% CI)* | 2.0 (0.75–5.5) | 2.1 (1.5–2.9) | 1.8 (1.2–2.5) | |
| Emphysema | Cases, N yes/total (%) | 2/131 (1.5) | 96/819 (11.7) | 105/952 (11.0) | 0.3 |
| | Controls, N yes/total (%) | 13/677 (1.9) | 32/900 (3.6) | 17/522 (3.3) | |
| | OR (95% CI)* | 0.69 (0.14–3.5) | 2.0 (1.3–3.3) | 2.2 (1.2–3.9) | |
| COPD‡ | Cases, N yes/total (%) | 8/130 (6.2) | 224/808 (27.7) | 277/943 (29.4) | 0.4 |
| | Controls, N yes/total (%) | 29/672 (4.3) | 84/893 (9.4) | 61/517 (11.8) | |
| | OR (95% CI)* | 1.5 (0.60–3.6) | 2.7 (2.0–3.7) | 2.3 (1.7–3.2) | |
| Asthma in males † | Cases, N yes/total (%) | 0/29 (0.0) | 28/714 (3.9) | 27/770 (3.5) | 0.3 |
| | Controls, N yes/total (%) | 22/395 (5.6) | 39/794 (4.9) | 12/418 (2.9) | |
| | OR (95% CI)* | 0.44 (0.24–0.82) | 0.70 (0.31–1.6) | |

*OR = odds ratio, CI = confidence interval. Adjusted for study age, sex, region, bronchitis (unless main effect or COPD), emphysema (unless main effect or COPD) and pneumonia for never smokers and also pack-years and amount of cigarette smoking (average packs/day) for smokers.
‡COPD = chronic obstructive pulmonary disease (chronic bronchitis and/or emphysema).
LRT = likelihood ratio test.
†OR = 0.76 (95% CI = 0.26–2.2) in female never smokers and 1.7 (95% CI = 0.59–5.1) in female ever smokers, LRT p-value = 0.2.
doi:10.1371/journal.pone.0007380.t003
among lighter smokers may suggest that chronic bronchitis and smoking share some molecular features, possibly involving inflammation. We can speculate that among lighter smokers both chronic bronchitis and smoking strongly contribute, while at heavier smoking levels some “saturation” occurs so that the contribution of chronic bronchitis to lung cancer appears less prominent. To fully evaluate these factors in concert with molecular and genetic markers (which for example, may assess inflammation and associated genes), larger studies in consortial settings will be required. Taken together, our data suggest that contribution of chronic bronchitis to lung cancer appears less heavier smoking levels some “saturation” occurs so that the magnitude of the risk ratios varied widely by study [41]. Most previous studies of asthma and lung cancer did not account for negative confounding by chronic bronchitis and emphysema. Of two that did, one found an OR of 1.5 (95% CI = 1.0 – 2.2) for asthma and risk of lung cancer after adjusting for chronic bronchitis and emphysema [37]. This study was conducted in nonsmoking women, however, and is therefore not comparable to ours since we found an inverse association only among males. The other study was conducted in males and females and found an OR of 1.1 (95% CI = 1.0 – 1.2) for asthma only and 0.73 (95% CI = 0.65 – 0.83) for both asthma and hay fever and lung cancer mortality. Our results were unaffected by adjustment for additional smoking variables, including environmental tobacco smoke, and support several studies that found inverse associations with asthma, eczema, and hay fever [15,40,42–44]. Although previous studies of the time from diagnosis of asthma to diagnosis of lung cancer have been inconsistent [37–40], we found that asthma was consistently inversely associated whether it was diagnosed within 5 years or more than 15 years prior to lung cancer.

Several potential explanations have been hypothesized for an inverse association between asthma and lung cancer [45]. Asthmatics might avoid smoking and other deleterious exposures that could trigger their asthma symptoms. Avoidance of such exposures may subsequently decrease their risk of lung cancer. However, we carefully adjusted for smoking and saw no consistent trends for asthma by smoking status. Often asthmatics are administered allergy medications (antihistamines, decongestants, corticosteroids, bronchodilators, antibiotics, etc.) over long periods of time due to the chronic nature of asthma. Although the potential impact of these medications on lung carcinogenesis is unclear, antibiotics, for example, might eliminate lung pathogens postulated to increase risk of lung cancer, such as Chlamydia pneumonia [46]. Finally, the “immunesurveillance hypothesis” suggests that asthma may stimulate the immune system such that it is better able to detect and destroy cancer cells [45]. That the inverse association is limited

### Table 4. Associations of lung cancer with lung disease diagnosed at least one year prior and lung cancer in the Environment And Genetics in Lung cancer Etiology case-control study restricted to current smokers (968 cases, 524 controls) and stratified by smoking status (tertiles among controls).

| Smoking Variable | Chronic bronchitis | Emphysema | COPD | Asthma in males |
|------------------|-------------------|-----------|------|-----------------|
|                  | OR (95% CI)*      | LRT p-value | OR (95% CI)* | LRT p-value | OR (95% CI)* | LRT p-value |
| Pack-years       |                   |           |             |               |            |             |
| < 14.4           | 5.0 (1.5 – 16.4)  | < 0.001   | 3.5 (0.26 – 4.5) | 0.05    | 5.0 (1.7 – 15.2) | < 0.001 |
| 14.4 – 34.5      | 2.1 (1.1 – 4.1)   |           | 1.5 (0.52 – 4.0) | 0.07    | 2.4 (1.3 – 4.3)   |           |
| ≥ 34.5           | 1.3 (0.81 – 2.0)  |           | 2.7 (1.3 – 5.6) | 0.07    | 1.9 (1.2 – 3.0)   |           |
| Intensity         |                   |           |             |               |            |             |
| (average)        |                   |           |             |               |            |             |
| < 0.5            | 7.1 (2.0 – 25.5)  | < 0.001   | 2.5 (0.44 – 14.7) | 0.07    | 5.6 (1.9 – 16.4) | < 0.001 |
| 0.5 – < 1        | 1.3 (0.70 – 2.6)  |           | 3.2 (1.0 – 9.8) | 0.07    | 2.1 (1.2 – 3.9)   |           |
| ≥ 1              | 1.6 (0.99 – 2.5)  |           | 1.8 (0.88 – 3.7) | 0.07    | 2.0 (1.3 – 3.1)   |           |
| Duration (years) |                   |           |             |               |            |             |
| < 26             | 4.5 (1.5 – 13.2)  | 0.02      | 2.3 (0.20 – 28.0) | 0.08    | 6.2 (2.1 – 17.8) | 0.08    |
| 26 – < 40        | 3.3 (1.6 – 6.8)   |           | 1.2 (0.39 – 4.0) | 0.08    | 3.1 (1.6 – 6.1)   |           |
| ≥ 40             | 1.1 (0.70 – 1.7)  |           | 2.7 (1.4 – 5.5) | 0.07    | 1.7 (1.1 – 2.6)   | 0.77    |

### Notes

- OR = odds ratio, CI = confidence interval. Adjusted for study age, sex, region, bronchitis (unless main effect or COPD), emphysema (unless main effect or COPD), pneumonia, pack-years, and amount of cigarette smoking (average packs/day).
- LRT = likelihood ratio test, using continuous smoking variables.

- COPD = chronic obstructive pulmonary disease (chronic bronchitis and/or emphysema).
References

1. Parkin DM, Bray F, Ferlay J, Pisani P (2005) Global cancer statistics, 2002. CA Cancer J Clin 55: 74–108.

2. Thun MJ, Henley SJ, Burns D, Jamal A, Shanks TG, et al. (2006) Lung cancer death rates in lifelong nonsmokers. J Natl Cancer Inst 98: 691–699.
