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Tobacco smoking as a risk factor of bronchioloalveolar carcinoma of the lung: pooled analysis of seven case–control studies in the International Lung Cancer Consortium (ILCCO)

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Abstract
Background The International Lung Cancer Consortium (ILCCO) was established in 2004, based on the collaboration of research groups leading large molecular epidemiology studies of lung cancer that are ongoing or have been recently completed. This framework offered the opportunity to investigate the role of tobacco smoking in the development of bronchioloalveolar carcinoma (BAC), a rare form of lung cancer.

Methods Our pooled data comprised seven case–control studies from the United States, with detailed information on tobacco smoking and histology, which contributed 799 cases of BAC and 15,859 controls. We estimated the odds ratio of BAC for tobacco smoking, using never smokers as a referent category, after adjustment for age, sex, race, and study center.

Results The odds ratio of BAC for ever smoking was 2.47 (95% confidence interval [CI] 2.08, 2.93); the risk increased linearly with duration, amount, and cumulative cigarette smoking and persisted long after smoking cessation. The proportion of BAC cases attributable to smoking was 0.47 (95% CI 0.39, 0.54).

Conclusions This analysis provides a precise estimate of the risk of BAC for tobacco smoking.

Keywords Lung cancer · Bronchioloalveolar carcinoma · Tobacco smoking
Introduction

Tobacco smoking is the most important cause of lung cancer, being responsible for an estimated 80–90% of cases in most populations of the world [1]. The carcinogenic effect of tobacco smoking on different histological types has been investigated in several studies, which typically included the most frequent types: a stronger risk has been repeatedly reported for squamous cell carcinoma and small cell carcinoma than for adenocarcinoma [2], while the risk of large cell carcinoma, which has been investigated less frequently, seems intermediate [3]. Data on other, rarer histological types are sparse and often based on a small series of cases leading to imprecise risk estimates.

Bronchioloalveolar carcinoma (BAC) of the lung is a form of adenocarcinoma characterized by growth of neoplastic cells along the alveolar structures with limited invasion of the blood vessels, the stroma, or the pleura. A mucinous and a non-mucinous variants are distinguished, the latter being more frequent. Distinction between BAC and other forms of lung adenocarcinoma is often difficult, and cancers, in particular those of larger size, frequently display mixed histologies [4]. BAC is considered a relatively infrequent form of lung cancer, but population-based data on incidence are scant. In the United States, age-adjusted incidence rates in the 1970s and 1980s were between 1 and 2 per 100,000, with little differences between sexes and races [5]. Reviews of series of patients from single institutions suggested an increase in the proportion of BAC over total lung cancers [6, 7], but the limited data from population-based cancer registries support the lack of a trend in incidence [5, 8]. Specific features of the epidemiology of BAC include a comparable incidence in men and women (in several series the number of female cases outnumber that of male cases), a shift in the distribution toward early-stage lesions, and a better survival rates than for other histological types of lung cancer, which is not fully explained by differences in stage at diagnosis [9].

The rarity of this histological type complicates the analysis of its risk factors. A lower proportion of smokers among BAC cases when compared to other types of lung cancer has been reported in early studies [9–12], but only two epidemiological studies have provided a formal estimate of the risk of BAC among smokers relative to non-smokers. In a study of 87 cases from several US hospitals, Morabia and Wynder [13, 14] reported an odds ratio (OR) of BAC for current smoking of 3.9 (95% confidence interval 1.8, 8.7), an increase in OR for increasing duration and amount of smoking, and a protective effect of quitting. In a study of 21 cases from Louisiana, Falk and colleagues [5] reported an OR of 4.0 (95% CI 0.9, 18.8) for ever smoking. Other risk factors have not been adequately investigated.

Pooled analyses within a consortium of data collected in independently conducted studies represent a cost effective approach in generating a large series of cases and controls. We have therefore conducted a pooled analysis of tobacco smoking and risk of BAC within the framework of the International Lung Cancer Consortium (ILCCO), which includes completed and ongoing studies of molecular and genetic epidemiology of lung cancer [15], with the aim of providing a precise measurement of the association between tobacco smoking and BAC.

Methods

This pooled analysis comprises data from seven case–control studies from the United States (Table 1). These studies represent a subset of studies included in the ILCCO collaboration (http://ilcco.iarc.fr). The remaining studies participating in the ILCCO consortium either excluded by design rare histological types of lung cancer or enrolled less than 10 BAC cases. The seven studies included one study each from the University of California at Los Angeles (UCLA) [16], Harvard University (HU) [17], University of Hawaii (UH) [18], two studies from Wayne

Table 1 Characteristics of studies included in the pooled analysis of lung bronchioloalveolar carcinoma and tobacco smoking

| Study, location | Study design | Definition of ever smoker (cigarettes) | Response rate (%) in ca/co | Total number of lung cancer cases | Number of BAC cases | Number of controls | Special features |
|----------------|-------------|----------------------------------------|----------------------------|----------------------------------|---------------------|-------------------|------------------|
| UCLA, Los Angeles [16] | Population-based | ≥100 | 39/79 | 611 | 39 | 1,040 |
| HU, Boston [17] | Hospital-based | ≥100 | 85/55 | 2,253 | 204 | 1,529 |
| UH, Honolulu [18] | Population-based | ≥185 | 64/62 | 635 | 38 | 588 |
| WSU1, Detroit [19] | Population-based | ≥100 | 55/71 | 526 | 50 | 460 | Women |
| WSU2, Detroit [20, 21] | Population-based | ≥100 | 66/93 | 1,006 | 35 | 1,184 | EO |
| Mayo [22] | Hospital-based | ≥100 | 87/84 | 5,698 | 280 | 2,269 |
| AHF [23, 24] | Hospital-based | ≥100 | 92/93 | 5,130 | 153 | 4,942 |

BAC bronchioloalveolar carcinoma, ca cases, co controls, EO early-onset cases
Results

Overall, 799 cases of BAC and 15,859 controls were included in the pooled analysis. Their demographic characteristics are summarized in Table 2. A total of 514 cases (64.3%) and 5,779 controls (48.1%) were women. The median age of cases was 65 years (interquartile range 56–73 years) and that of controls was 56 years (interquartile range: 45–65 years). Table 3 reports the results of the analysis of tobacco smoking. The OR for ever smoking was 2.47 (95% CI 2.08, 2.93); it was 2.51 (95% CI 2.09, 3.01) for current smoking and 2.35 (95% CI 1.90, 2.92) for former smoking. The study-specific ORs for ever smoking are presented in Fig. 1: they ranged from 1.12 in the UCLA study to 3.90 in the AHF study; the p-value of the test for between-study heterogeneity in OR was 0.01. The summary estimate of OR for BAC based on a meta-analysis fixed effects model was 2.38 (2.00, 2.85); the summary OR based on a random-effects model was 2.20 (95% CI 1.51, 3.20). A linear trend was observed for amount of smoking (OR for an increase in 10 cigarettes/day 1.32, 95% CI 1.27, 1.38; p-value of test for between-study heterogeneity 0.07),
duration of smoking (OR for a 10-year increase 1.25, 95% CI 1.20, 1.30; between-study heterogeneity p-value 0.01), and cumulative smoking (OR for an increase in 10 pack years 1.29, 95% CI 1.24, 1.34).

Table 4 presents the pooled results for ever smoking stratified by sex, age at diagnosis, and education level. No heterogeneity was suggested with respect to age sex or education level. The proportion of BAC attributable to ever smoking tobacco was 0.47 (95% CI 0.39, 0.54). It was 0.74 (95% CI 0.17, 0.66) in men and 0.37 (95% CI 0.24, 0.48) in women.

Discussion

Our analysis adds strong evidence to the notion that BAC is a form of lung cancer associated with tobacco smoking. The current analysis also provides strong evidence on a beneficial effect of quitting tobacco smoking, as it has been shown for lung cancer in general and for the major histological types [29].

Our results are quantitatively consistent with those of the two epidemiological studies of BAC available in the literature [5, 13, 14]: a meta-analysis of the results for current smoking for the three studies resulted in a p-value for heterogeneity of 0.7.

We acknowledge several limitations to our study. We were not able to perform a systematic pathology review of the cases, and the possibility of misdiagnosis remains open for some cases. However, misclassification is most likely to occur with other forms of adenocarcinoma [4], a type of lung cancer that is less strongly associated with tobacco smoking than other types, and diagnoses of well-differentiated lung cancer have been found to be reproducible [30, 31]. The proportion of BAC over total lung cancer cases varied from over 9% in the HU and WSU1 studies to 3% in the AHF study. A validation of BAC diagnosis was
performed only in some of studies included in this pooled analysis; however, the study-specific results presented in Fig. 1 do not suggest an important role for diagnostic misclassification, since the magnitude of the excess risk did not appear to correlate with validation of pathological diagnosis.

The lack of histological verification also pre-empted us from distinguishing between the two main types of BAC, namely mucinous and non-mucinous. This is unfortunate because the molecular alterations seem to differ between the two types, with a higher proportion of codon 12 KRAS mutations in the mucinous type and, conversely, a higher proportion of TP53 mutations in the non-mucinous type [32–35]. The high proportion of EGFR mutations in BAC, when compared to other types of lung adenocarcinoma [36], is consistent with a comparatively lesser etiologic role of tobacco smoking in the former type of neoplasm.

An additional potential limitation, which is common to retrospective epidemiological studies, is recall bias, i.e., lung cancer cases over-reporting tobacco smoking when compared to controls, either because of better recall or because they are trying to explain their disease. However, the internal consistency of our results (dose–response relation with amount and duration of smoking, effect of long-term quitting, lack of heterogeneity by sex, age, or education) argues against a strong role of recall bias.

The main strength of our study lies in its size, as it included more than seven times the total number of BAC cases included in previous epidemiological studies on the effect of tobacco smoking on this form of lung cancer. The high quality of participating studies and the validity of the information on exposure and outcome are confirmed by the consistency of inter-study risk estimates.

No results have been reported on risk of BAC after cessation of smoking. The available evidence points toward a more rapid decrease in risk with increasing time since cessation for squamous cell carcinoma than for adenocarcinoma [29]. The similarities between BAC and adenocarcinoma might explain the relatively weak effect of quitting we observed in our analysis.

In conclusion, our pooled study resulted in a twofold increased risk of lung BAC in ever smokers when compared to never smokers, and in evidence of a dose–response

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**Fig. 1** Study-specific odds ratios (and 95% confidence intervals) of lung bronchioloalveolar carcinoma for ever tobacco smoking. The combined odds ratio is based on a random-effects model meta-analysis.

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**Table 4** Odds ratio of bronchioloalveolar carcinoma for ever tobacco smoking in the pooled analysis, stratified by sex, age at diagnosis, and education

| Stratum               | OR  | 95% CI          |
|-----------------------|-----|-----------------|
| **Sex**               |     |                 |
| Men                   | 2.10| 1.61, 2.91      |
| Women                 | 2.52| 2.01, 3.08      |
| Test for heterogeneity, p-value | 0.87 |                 |
| **Age**               |     |                 |
| ≤60 years             | 1.48| 0.97, 2.26      |
| 50–60 years           | 2.65| 1.78, 3.95      |
| 60–70 years           | 2.39| 1.77, 3.23      |
| >70 years             | 2.73| 1.99, 3.70      |
| Test for heterogeneity, p-value | 0.12 |                 |
| **Education**         |     |                 |
| Lower than college    | 3.05| 2.35, 3.98      |
| College of higher     | 2.39| 1.88, 3.05      |
| Test for heterogeneity, p-value | 0.18 |                 |

CI confidence interval, OR odds ratio, adjusted for age, gender, race, and study center.
relation according to duration and amount of smoking. Forty-seven percent of BAC cases in the study population would be attributable to the habit. This is the most precise estimate of the risk of BAC for tobacco smoking available in the literature and supports the notion of an association between tobacco smoking.

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