

Lung Cancer and Cryptogenic Fibrosing Alveolitis

A Population-based Cohort Study

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EXHIBIT

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Cryptogenic fibrosing alveolitis has been reported to be associated with an increased risk of lung cancer. However, it has recently become apparent that cigarette smoking may be a risk factor for cryptogenic fibrosing alveolitis as well as for lung cancer, and so may confound the association between these conditions. We have therefore estimated the independent increase in lung cancer incidence in patients with cryptogenic fibrosing alveolitis compared with the general population in a population-based cohort study involving 890 subjects with cryptogenic fibrosing alveolitis and 5,884 control subjects drawn from the United Kingdom General Practice Research Database. The incidence of lung cancer was markedly increased among patients with cryptogenic fibrosing alveolitis (rate ratio [RR] 7.31, 95% confidence interval [95% CI] 4.47 to 11.93, $p < 0.001$), and adjustment for previous smoking history had little effect on this odds ratio (adjusted RR: 8.25, 95% CI 4.70 to 11.48, $p < 0.001$). This increase in lung cancer incidence remained when the analysis was restricted to current smokers (RR 7.36, 95% CI 1.54 to 35.19, $p = 0.012$). This study provides clear evidence that the incidence of lung cancer is increased in patients with cryptogenic fibrosing alveolitis, and that this effect is independent of the effect of cigarette smoking. Hubbard R, Venn A, Lewis S, Britton J. Lung cancer and cryptogenic fibrosing alveolitis: a population-based cohort study.

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Cryptogenic fibrosing alveolitis is now the commonest interstitial lung disease seen in the United States, and appears to be increasing in prevalence in many developed countries (1, 2). For some years now it has been reported that the risk of lung cancer is high in patients with cryptogenic fibrosing alveolitis (3, 4). This observation is important both to the prognosis and counseling of patients with cryptogenic fibrosing alveolitis, and may also be relevant to understanding the causes of lung cancer. However, not all studies have confirmed this finding (5), and recent evidence that cigarette smoking may be an independent risk factor for cryptogenic fibrosing alveolitis (6-8) raises the possibility that the association between these two conditions may be due to confounding by smoking.

To clarify the question of whether the incidence of lung cancer is increased in patients with cryptogenic fibrosing alveolitis independently from the effects of cigarette smoking, we have carried out a cohort study using longitudinal data for 890 patients with cryptogenic fibrosing alveolitis and 5,884 control subjects drawn from the UK General Practice Research Database.

METHODS

The General Practice Research Database (GPRD) is the largest primary care population database in the United Kingdom (9, 10), comprising data from over 7 million patients. General practices (primary care centers) participating in the database are required to ensure that their patient records include details of at least 95% of prescribing and morbidity events. Once this level of data quality has been achieved, the practice is assigned an "up to standard" date, and thereafter monthly checks of data quality are carried out. Practices that do not comply with this quality control are removed from the database. The data for this study were extracted in April 1998 and set up as a relational database using Microsoft Access.

To establish a cohort of patients with cryptogenic fibrosing alveolitis, all subjects with a diagnosis of cryptogenic fibrosing alveolitis recorded anywhere in their GPRD record were identified. The date of diagnosis was defined as the date of the first mention of cryptogenic fibrosing alveolitis. A control cohort was established by identifying the six individuals of the same sex, attending the same general practice and closest in age to each subject. For the purpose of standardizing data extraction, each control subject was assigned an "equivalent date of diagnosis" to match his or her case. Because the prognosis of patients with cryptogenic fibrosing alveolitis in association with a connective tissue disease may be better than that for patients without connective tissue disease (11), all subjects in both cohorts with a recorded diagnosis of connective tissue were excluded.

To validate the diagnosis of cryptogenic fibrosing alveolitis in cases, copies of hospital letters and discharge summaries sent to the general practitioners were obtained for a random sample of 36 cases (the expense of obtaining these data limited the sample size for diagnostic validation). Cases of cryptogenic fibrosing alveolitis were considered to be valid if the attending consultant physician reported the diagnosis to be cryptogenic fibrosing alveolitis, and in addition reported that inspiratory crackles were audible on auscultation and that the chest radiograph appearance suggested cryptogenic fibrosing alve-

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olitis. We did not include histological confirmation from an open lung biopsy in our diagnostic criteria because in clinical practice only a small minority of patients undergo this procedure (1, 6). The accuracy of a recorded diagnosis of malignant disease, including lung cancer, has been shown to be high in the GPRD (12) and so we did not attempt to verify the diagnoses of lung cancer in this study.

Data on the earliest recorded entry for smoking habit before to the date of diagnosis and diagnosis of lung cancer were extracted from the data set. Smoking habit was recorded as nonsmoker, current smoker, ex-smoker, pipe or cigar smoker, or missing. For some subjects more detailed information on the number of cigarettes smoked each day was available, and this was grouped as 1 to 10 per day, 11 to 20 per day, and greater than 21 per day. For each subject, the person-years contributed to the cohort was calculated as the difference between the date of registration at the practice or the practice date "up to standard," whichever was the later, and the date of diagnosis of lung cancer or date of last data collection.

We performed a biological validation of the smoking data by estimating the rate ratios (RR) for the association between smoking habit and lung cancer within the control cohort only, using Cox regression with adjustment for sex and age (in quartiles). We compared the smoking habits of patients with cryptogenic fibrosing alveolitis and control subjects using conditional logistic regression. We compared the lung cancer incidence rate between the two cohorts using Cox regression, controlling for age and sex and adding multiplicative terms as appropriate to test for possible interactions with age (in quartiles) and sex. To determine whether smoking habit confounded the association between cryptogenic fibrosing alveolitis and lung cancer, we performed two additional analyses; first we added the variable for smoking status to the model, and second we restricted our analysis to include only subjects who were reported to be current smokers. In the second of these analyses we also adjusted for the number of cigarettes smoked per day. All analyses were conducted using STATA and likelihood ratio tests were used for all tests of significance. For Cox regression models the proportional hazards assumption was tested using the diagnostic section within STATA (phtest 1).

The study protocol was reviewed and approved by the General Practice Research Database ethics committee.

RESULTS

A total of 998 subjects with cryptogenic fibrosing alveolitis and 5,988 control subjects were identified in the data set. One hundred and eight (10.8%) subjects with cryptogenic fibrosing alveolitis and 104 (1.7%) control subjects had a diagnosis of a connective tissue disease recorded and were excluded from subsequent analyses, leaving cohorts of 890 and 5,884. The mean

($\pm$ SD) person-years contributed to the cohort was 5.0 ± 1.9 for subjects with cryptogenic fibrosing alveolitis and 6.0 ± 1.7 for control subjects. The median age of subjects with cryptogenic fibrosing alveolitis was 71 yr (interquartile range 64 to 78 yr) and 553 (62%) were male.

We were able to obtain copies of hospital letters and discharge summaries for 20 of the subsample of 36. The reason for unavailability was death in three cases, patients having left the practice in five cases, and lack of response from the practice in eight cases. Review of the available records confirmed the diagnosis in all but one case, in which the patient had a diagnosis of extrinsic allergic alveolitis.

Smoking data were available for 624 subjects with cryptogenic fibrosing alveolitis (70%) and 3,752 control subjects (64%). There were 53 cases (0.9%) of lung cancer among the control subjects, 50 of which fell within the period of data up to standard. As expected, there was a marked increased incidence of lung cancer in current smokers (RR 9.53, 95% confidence interval [95% CI] 3.81 to 23.86) and ex-smokers (RR 5.89, 95% CI 1.78 to 19.47) compared with the nonsmokers (Table 1). In addition there was a strong dose-response relationship between the occurrence of lung cancer and the number of cigarettes smoked per day within the current smokers (Table 1). Overall there was a small and nonsignificant increase in the proportion of current and ex-smokers among the subjects with cryptogenic fibrosing alveolitis compared with control subjects (Table 2). There was no evidence of a dose-response relationship between number of cigarettes smoked per day in current smokers and risk of cryptogenic fibrosing alveolitis.

A total of 39 cases of lung cancer were identified among the subjects with cryptogenic fibrosing alveolitis (4.4%), 38 of which were within the period of data up to standard. The RR for the association between lung cancer and cryptogenic fibrosing alveolitis was 7.31 (95% CI 4.47 to 11.93, $p < 0.001$). This RR was not reduced when smoking status was added to the model (RR 8.25, 95% CI 4.70 to 11.48), and there was no evidence of interaction with age or sex. When the analysis was restricted to current smokers alone, the association between cryptogenic fibrosing alveolitis and lung cancer remained (RR 7.36, 95% CI 1.54 to 35.19, $p = 0.012$) (Table 3), and this RR was not appreciably altered by adjusting for the number of cigarettes smoked each day (RR 6.67, 95% CI 1.19 to 37.52).

DISCUSSION

This study provides strong evidence that the risk of lung cancer is increased markedly in patients with cryptogenic fibrosing alveolitis, and that this effect is independent of smoking habit. The cases in this study represent the largest case population described in the literature to date. We validated the diagnosis of cryptogenic fibrosing alveolitis according to our pre-

TABLE 1
SMOKING STATUS AND RISK OF LUNG
CANCER IN THE CONTROL SUBJECTS

Smoking Status	Lung Cancer (%)	Rate Ratio*	95% CI
Nonsmoker (n = 2,409)	8 (0.3)	1	
Current smoker (n = 909)	21 (2.3)	9.53	3.81 to 23.86
Ex-smoker (n = 327)	5 (1.5)	5.89	1.78 to 19.47
Pipe or cigar smoker (n = 107)	2 (1.9)	6.92	1.36 to 35.21
Missing data (n = 2,132)	17 (0.8)		
Likelihood ratio test $p < 0.0001$			
Current smokers with data on number of cigarettes smoked per day (n = 868)			
1-10 cigarettes per day (n = 395)	6 (1.5)	1	
11-20 cigarettes per day (n = 376)	10 (2.7)	1.98	0.67 to 5.88
> 21 cigarettes per day (n = 95)	5 (5.2)	5.40	1.45 to 20.05
Likelihood ratio test for trend $p = 0.016$			

* RRs adjusted for age and sex.

TABLE 2
SMOKING STATUS AND RISK OF
CRYPTOGENIC FIBROSING ALVEOLITIS

Smoking Status	Patients (%) (n = 890)	Control Subjects (%) (n = 5,884)	Odds Ratio	95% CI
Nonsmoker	382 (43)	2,409 (41)	1	
Current smoker	169 (19)	909 (15)	1.13	0.91 to 1.40
Ex-smoker	64 (7)	327 (6)	1.17	0.85 to 1.61
Pipe or cigar smoker	9 (1)	107 (2)	0.51	0.25 to 1.03
Missing data	266 (30)	2,132 (36)		
Likelihood ratio test $p = 0.08$				

TABLE 3
ASSOCIATION BETWEEN CRYPTOGENIC FIBROSING ALVEOLITIS
AND LUNG CANCER BY SMOKING STATUS

Smoking Status	Number (%) of Cases of CFA with Lung Cancer	Number (%) of Control Subjects with Lung Cancer	Rate Ratio	95% CI	p Value
Nonsmokers	12 (3.1%)	8 (0.3%)	14.83	3.23 to 68.10	0.001
Ex-smokers	2 (3.1%)	5 (1.5%)	1.00	0.06 to 15.99	0.9
Pipe and cigar smokers	0	2 (1.9%)			
Current smokers	15 (8.9%)	21 (2.3%)	7.36	1.54 to 35.19	0.012

Definition of abbreviations: CFA = cryptogenic fibrosing alveolitis.

defined criteria in a small subgroup of this data set, and found the proportion of true positives to be high at 95%. Cryptogenic fibrosing alveolitis is an uncommon disease and general practitioners will usually have only limited experience of it. It is therefore unlikely that patients will be given the diagnosis without secondary referral to a pulmonary specialist, and so the high validity of a positive diagnosis is not unexpected. This finding is also consistent with previous studies of the accuracy of death certification and hospital discharge summaries which have demonstrated that patients assigned a diagnosis of cryptogenic fibrosing alveolitis usually do have the disease (13, 14). We were unable to assess how many control subjects had undiagnosed cryptogenic fibrosing alveolitis (the false-negative rate), but given that approximately 1 in 500 people die with cryptogenic fibrosing alveolitis (2) it is likely that there were some undiagnosed cases. The effect of these missed cases will, however, be small and will tend to bias the association between cryptogenic fibrosing alveolitis and lung cancer toward unity.

The distribution of reported smoking habits in our data set is similar to those published for other studies of the GPRD (12, 15), but on closer inspection they appear incompatible with the likely lifetime smoking habits of a U.K. population with a median age of 70. Although the proportion of current smokers reported in the control group is consistent with recent data from the general household survey (20% for people age 60 yr and older), the level of ex-smokers (6%) is not (16). Immediately after the Second World War the majority of men in the U.K. were smokers, and even as late as the mid 1970s 45% of men and 38% of women were smokers (16). The expected proportion of ex-smokers is therefore in the region of 40 to 50%, so it seems likely that the majority of ex-smokers have been misclassified as nonsmokers.

As expected we found strong associations within the control cohort between both current and ex-smoking, and lung cancer. Although the size of these effects was large, they are likely to underestimate the true effect of smoking if there was extensive misclassification of ex-smokers as nonsmokers. However, because the dose-response analysis of the number of cigarettes smoked per day was restricted to current smokers alone, estimates arising from this analysis will not be subject to this misclassification problem, and therefore provide a more accurate assessment of the increased risk of lung cancer faced by heavy smokers in comparison to light smokers.

In contrast to the results of previous studies (6-8), our results show only small increase in risk of cryptogenic fibrosing alveolitis for both current and former smokers, which did not reach the conventional level of statistical significance. There are two potential explanations for this finding; either that there is no effect of cigarette smoking and that the previous findings (6-8) were the result of recall or selection bias, or, perhaps more likely, that the effect of smoking is relatively small (6-8) and our estimate of effect was biased toward unity by misclassification of ex-smokers as nonsmokers.

We did, however, find a marked increase in the incidence of lung cancer among patients with cryptogenic fibrosing alveolitis. Adjustment for the effects of smoking status in the statistical model had little impact on this increased risk, although because of likely misclassification we cannot be sure that all of the effect of smoking has been allowed for in this analysis, and thus the potential for residual confounding remains. However, because the association between lung cancer and cryptogenic fibrosing alveolitis we found is strong (RR 7), and the associations between cryptogenic fibrosing alveolitis and smoking demonstrated in previous studies (6-8) are weak (odds ratios less than two), in fact residual confounding is unlikely to have a major impact on the association between cryptogenic fibrosing alveolitis and lung cancer. To resolve this issue, however, we restricted our analysis to current smokers alone, and in this analysis the increased incidence of lung cancer among subjects with cryptogenic fibrosing alveolitis remained.

The majority of patients with cryptogenic fibrosing alveolitis are under review by pulmonary specialists and will be more likely to have chest radiographs than the general public. Lung cancer may therefore be more likely to be diagnosed earlier in patients with cryptogenic fibrosing alveolitis, but it seems unlikely that this can account for the strength of association we observed. Furthermore, the fact that the association is unchanged in current smokers, in whom investigation of symptoms suggestive of lung cancer is likely to be relatively thorough for both cases and control subjects, suggests that this form of ascertainment bias did not have a major effect.

Cryptogenic fibrosing alveolitis produces chronic inflammation within the lungs over many years, and so if the parallel is drawn with the increased risk of cancer of the colon observed in patients with ulcerative colitis (17), an increase in lung cancer is perhaps not surprising. It seems likely that this increase in malignancy is secondary to the chronic inflammatory and fibrotic processes that occur in the lung, just as the increased risk of lung cancer after asbestos exposure tends to be most marked in areas of lung fibrosis (18). It has been speculated that the chronic inflammation in the lung produces extensive DNA damage leading in turn to overexpression and mutation of the p53 gene resulting in carcinogenesis (19). Another possible explanation is that cryptogenic fibrosing alveolitis and lung cancer are both caused by a common etiological agent. Further research is required to determine the precise mechanisms that lead to the dramatic increase in lung cancer in patients with cryptogenic fibrosing alveolitis.

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