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ORIGINAL RESEARCH

Recent trends in lung cancer and its association with COPD: an analysis using the UK GP Research Database

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Abstract

Background: The association between lung cancer and COPD has not been investigated in the primary care setting.

Method: We determined the recent trends of lung cancer in COPD patients in the UK during the period 1991-2004, by investigating the population aged 45 and over in the General Practice Research Database.

Results: The annual-incidence rates of lung cancer per 10,000 person-years were at least four-fold higher in patients with prior COPD (increasing from 45 to 64 in men; 29 to 48 in women) compared with the general population (from 10 to 15 in men; 5 to 10 in women). These lung cancer trends had significant annual increases that were similar in men (5%) and in women (5.5%) with prior COPD; in contrast, the annual increases of lung cancer incidence rates in the general population differed by gender, being 4% in men but double in women (8%). The three-year survival for lung cancer patients among those with prior COPD was almost half that of the general population (15% versus 26%; p<0.01) and the highest mortality was observed in men aged 45-64 (83.79 per 100 person-years; 95% CI: 69.66-97.92).

Conclusion: These results support the association of COPD and lung cancer observed in other settings.

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Introduction

Associations between lung cancer and acquired lung diseases that obstruct airflow including chronic obstructive pulmonary disease (COPD) have been noted, although a recent review has highlighted the many issues that await resolution after more than 60 years of research on this topic.[1] Nevertheless, a substantial body of evidence suggests that COPD or impaired lung function is associated with the occurrence of lung cancer.[2-4] Although cigarette smoking is the principal cause of both COPD and lung cancer, many studies have found evidence of the role of COPD in the development of lung cancer, independent of smoking.[3, 5-10] One of these studies estimated the prevalence of COPD in lung cancer patients as between 50-65%.[7] At values of forced expiratory volume in one second (FEV_1) lower than 70% predicted and after adjusting for confounders such as smoking, the excess risk of lung cancer due to COPD was estimated at 2.23 in men and 3.94 in women. Studies have also shown that the risk of developing lung cancer does not immediately disappear after smoking cessation – perhaps explaining why, in the USA, lung cancer now occurs in as many former smokers as current smokers.[11]

In a landmark clinical and molecular study, the expression of a number of putative oncogenes and tumour suppressor genes in the airway epithelial cells of smokers did not return to normal for decades after smoking cessation, although many others (especially the antioxidant and drug-metabolising genes) did so within two years.[12] The same study suggests that there may also be a gene expression profile that is characteristic of COPD, having identified a number of genes

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whose expression levels correlate in a negative or positive fashion with FEV_1 that are not altered in subjects with lung cancer. The reason why some smokers develop COPD while others do not remains unclear, as is the reason why some smokers are free of both COPD and lung cancer.

The UK General Practice Research Database (GPRD), an automated database that covers about 5% of the population, has the potential to help us better define the epidemiology of lung cancer in the UK general population as well as among those people with COPD. Lung cancer has been investigated in two previous studies using the GPRD: one examined patients with cryptogenic fibrosing alveolitis and its association with lung cancer;[13] the other was a case-control study that explored whether non-steroidal anti-inflammatory drug treatment protects against the commoner cancers in the UK.[14] Furthermore, previous studies have also described the clinical epidemiology of COPD using the GPRD in terms of trends of prevalence and incidence in the UK.[15-16]

The aim of our study was to describe the relationship between lung cancer and COPD in the UK primary care setting. We aimed to determine the trends in annual incidence of lung cancer in individuals already diagnosed with COPD and in those from the general population over a 15-year period in the GPRD.

Methods

The GPRD database has been described elsewhere.[17] It is a large, automated network of general practices in the UK that continues to provide a unique and continuous source of information on the overall health of the general population. It is therefore a valuable data source for the identification of incidence and prevalence of major diseases, analysis of treatment patterns and outcome for specific diseases, variations in prescribing patterns, and adverse reactions to drugs, among others. A growing number of studies conducted in the GPRD database have been widely reported elsewhere, and the GPRD update as of December 2006 was used in this study.[18-21] This study was conducted within a research protocol approved by the Independent Scientific Advisory Committee (ISAC) of the GPRD.

Case definitions

The study period for inclusion was between 1st January 1991 and 31st December 2004, and the survival analyses were extended up to 2006. Validated OXMIS/READ codes in the GPRD (see http://www.gprd.com) were used to identify patients with incident diagnosis of COPD and/or lung cancer during the study period. Furthermore, only patients aged 45 years and older at diagnosis, from practices whose data were classified as 'up to standard' in the GPRD, were included. We excluded patients with asthma codes identified at any time before COPD, and anyone with cystic fibrosis.

Study design

Two cohorts were determined. We defined a cohort of GPRD participants who were at risk of lung cancer at the start of our study period, and another cohort of GPRD participants with COPD who were similarly at risk of lung cancer. Patients with a prior lung cancer diagnosis before cohort entry were excluded in both cohorts because of our interest in the incidence (i.e. development) of lung cancer in the COPD and in the general population cohorts. In each cohort, the individual's longitudinal medical records were reviewed, and for each year of the study period we identified patients who were diagnosed with lung cancer for the first time (i.e. incident cases).

Statistics

In the COPD cohort (i.e. to estimate lung cancer incidence in COPD), the date of the first OXMIS/READ code identifying incident physician-diagnosed COPD was used as time zero in the analysis. As COPD is a serious condition that needs regular medical management, an individual was considered censored if no GP contact was recorded 12 months after his/her last visit or medical contact – as was done in previous studies using the database.[18-21] In a similar way, censoring was applied when a patient either left the practice or died.

Annual lung cancer incidence rates per 10,000 patients (as 5-year moving averages) and mortality rates of lung cancer per 100 person-years were estimated by gender, calendar year from 1991 to 2004, and age, using standard techniques.[22] Log linear models were used to compare mortality distributions by gender and age.

Results

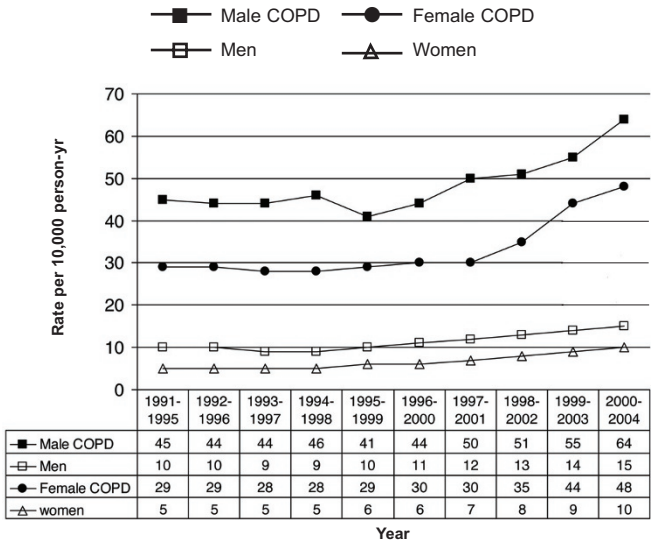
During the period 1st January 1991 to 31st December 2004, a total of 18,077 patients with incident diagnosis of lung cancer were identified in the GPRD from a population of 4,688,416 persons aged 45 and older who were free of the

Table 1. Characteristics of lung cancer patients, and of those with a prior diagnosis of COPD (Total population aged 45 or older=4,688,416; Incidence diagnosed COPD=42,188).

	Lung cancer	Lung cancer in those with prior COPD
Number	18,077	1,260
45-64 years, n (%)	4,783 (26.5)*	204 (16.2)
64+ years, n (%)	13,294 (73.5)*	1,056 (83.8)
Female, n (%)	7,262 (40.2)*	463 (36.8)
Mean age at diagnosis (SD)	71.1 (10.6)*	72.9 (8.7)

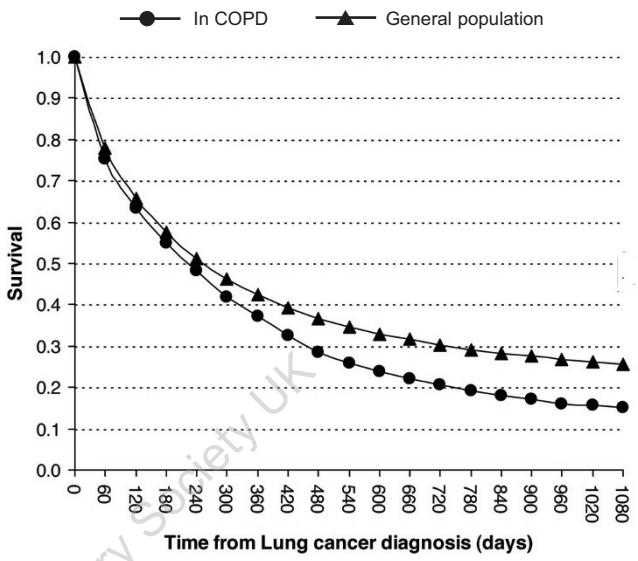
* P< 0.05 in comparison with prior COPD

Figure 1. Incidence (per 10,000) of lung cancer in the general population and in those with a prior diagnosis of COPD by gender: 5 year moving averages (1991-2004).



	1991-1995	1992-1996	1993-1997	1994-1998	1995-1999	1996-2000	1997-2001	1998-2002	1999-2003	2000-2004
Male COPD	45	44	44	46	41	44	50	51	55	64
Men	10	10	9	9	10	11	12	13	14	15
Female COPD	29	29	28	28	29	30	30	35	44	48
women	5	5	5	5	6	6	7	8	9	10

Figure 2. Three-year survival of lung cancer patients in the general population and in those with a prior diagnosis of COPD.



disease at the study start. Similarly, we identified 1,260 patients with lung cancer among those previously diagnosed with COPD (Table 1). The total number of incident-diagnosed COPD patients in the period was 42,188.

Women represented 40% of all lung cancer patients, and this percentage was slightly but significantly less among those with previous COPD (36.8%) (p=0.02). Among all patients, the average age at diagnosis of lung cancer was 71.1 (SD=10.6) and just over 26% of these were under 65 years of age. Among those with a previous diagnosis of COPD, average age was slightly but significantly older than in the general population at 72.9 years (SD=8.7), and significantly fewer were under 65 years of age (i.e. 16.2%; p<0.0001).

Annual incidence rates of lung cancer increased significantly over the study period in the general population from 10 to 15 per 10,000 in men and from 5 to 10 per 10,000 in women (Figure 1). Among those with a prior diagnosis of COPD, annual incidence rates were more than four-fold and five-fold higher than in the general population in men and women, respectively, increasing from 45 to 64 per 10,000 in men and from 29 to 48 per 10,000 in women. These trends indicated a narrowing of the gender gap in annual incidence among the general population (4.4% in men compared with 8.2% in women), but we found no gender differences in the average annual increase of lung cancer in those with prior COPD diagnosis (5% in men compared with 5.5% in women).

Figure 2 shows that, although the survival of lung cancer patients in the first three years since diagnosis was very low, survival was much lower among those with a prior diagnosis of COPD. Only about 15% of those with prior COPD diagnosis survived for three years compared with nearly 26% among all

Table 2. Mortality rates (per 100 person-years) in lung cancer patients, and of those with a prior diagnosis of COPD.

	Lung cancer	Lung cancer in those with prior COPD	Rate Ratio with 95% CI
Mean age at death (SD)	72. 5 (10.4)	73. 9 (8.7)	
Mortality rates (per 100 person-years) and 95% C.I.			
Female	40.88 (39.77 ,41.99)	75.13 (67.31 ,82.95)*	1.84 (1.65 ,2.05)*
Male	39.56 (38.69 ,40.43)	75.17 (69.33 ,81.01)*	1.90 (1.75 ,2.06)*
45-64	64.47 (62.14 ,66.80)	83.79 (69.66 ,97.92)*	1.30 (1.09 ,1.54)*
65+	36.13 (35.43 ,36.83)	73.95 (69.00 ,78.90)*	2.05 (1.91 ,2.19)*

* P< 0.05 in comparison with lung cancer patients without prior COPD

lung cancer patients. Indeed, mortality rates were significantly higher in those with prior COPD (rate ratios of 1.84; 95% CI: 1.65-2.05 in females and 1.90; 95% CI: 1.75-2.06 in men) and among the sub-group aged 65 or older, in which rates were twice those observed in the whole group (Table 2).

Mortality rates were similar among men and women with prior COPD (75.17; 95% CI: 69.33-81.01 versus 75.13; 95% CI: 67.31-82.95), as well as in the general population, (39.56; 95% CI: 38.69-40.43 versus 40.88.13; 95% CI: 39.77-41.99), respectively.

Discussion

Over the 14-year period (1991-2004) evaluated in this study, the incidence of lung cancer increased significantly, both in men and in women. Annual incidence rates of lung cancer were at least four-fold higher in patients with prior COPD when compared with the general population. Incidence trends of lung cancer indicated a significant narrowing of the gender gap in the general population, but among those with COPD there was no noticeable change in the gender gap. Although the three-year survival from diagnosis of lung cancer was very low, it was considerably lower in those with a prior COPD diagnosis. Lung cancer is more common in patients aged 65 and older – and among those with a prior diagnosis of COPD, lung cancer is diagnosed at an even later age.

COPD and lung cancer share many common pathophysiological features, and COPD patients are often considered at high risk of developing lung cancer.[23] In a prospective study, the risk of developing lung cancer was found to be associated with age, smoking and ventilatory status.[24] Primarily, the main risk factor for the onset of both diseases is cigarette smoking, but they probably also share a common familial component and environmental risk factors other than smoking.[25] Some common elements in the pathogenesis of COPD and lung cancer include genetic predisposition (p53, Rb, K-ras), peptides and endopeptidases (bombesin-like), inflammation and oxidants (cigarette smoking), and dysregulation of growth factor expression,[26] among others.

In a clinical review of a case series of 966 lung cancer patients admitted over a period of 24 years in Japan, 73 patients (7.5%) were diagnosed as having COPD; of these, 68 (93.2%) were men, and in 43 cases (58.9%) the tumours were squamous cell carcinomas.[27] A recent case-control study also conducted in Japan involving COPD patients matched to patients with benign respiratory diseases (as regards age, gender and smoking history) estimated the relative risk of cancer incidence as 2.32 (95% C.I: 1.24-4.27);[28] the study reported the most common cancers in COPD patients as being in the lung (18 cancers), the head and neck (15 cancers), and the urinary tract (6 cancers). The authors concluded that physicians should be alert to the development of malignancies in COPD patients, in the lung and other locations, so as to detect them at an early stage and administer proper treatment.

Another study also found an association between lung cancer and prior COPD which was assessed by lung function measurement.[29] The authors studied adult participants in the US First National Health and Nutrition Examination Survey, who had up to 22 years of follow-up. Subjects were classified as having moderate to severe obstructive lung disease at baseline if the ratio FEV_1 to forced vital capacity (FVC) was less than 0.70 and the FEV_1 was less than 80% of the predicted value. Incident cases of lung cancer during the follow-up period were studied. A total of 113 (2.0%) lung cancers occurred in the 5,402 adults in the cohort. In the proportional hazards model which was adjusted for age, gender, race, education, smoking status, and duration as well as intensity of smoking, the presence of moderate to severe obstructive lung disease was found to be associated with a higher risk of incident lung cancer (hazard ratio, 2.8; 95% CI: 1.8-4.4).

Although our study may be the first to find similar evidence of the association between lung cancer and COPD in the primary care setting, and although it includes a much longer follow-up and duration than any other, it has some notable limitations. Implementation of spirometry in primary care is not universal in the UK and elsewhere, and many GPs often only rely on a clinical diagnosis of chronic bronchitis and emphysema without performing spirometry – which is contrary to international COPD guidelines which require post-bronchodilator spirometry for the diagnosis and staging of COPD.[30] The GPRD data lacked quantitative information on tobacco consumption, and lung cancer pathology is not systematically recorded. Consequently, we have not addressed the role of smoking as a confounding factor in the association found between COPD and lung cancer incidence. Nevertheless, both lung cancer and COPD have been previously studied in the GPRD and the findings reported.[13-16, 18-21] Indeed, the higher risk of lung cancer we found among those with COPD aged 65 or older has also been reported elsewhere.[29] In a large, recent study, Wilson *et al*.,[31] using CT scan together with spirometry to search for emphysema and lung cancer in 3,638 smokers, were intrigued to find absence of a dose-response relationship between smoking intensity and lung cancer among those with moderate to severe emphysema – a finding which has led to the hypothesis that COPD patients may have some host or susceptibility factors that protect them from developing cancer in general (having taken 30 or more years of exposure to tobacco to develop COPD), whereas in those who are more susceptible to developing cancer, lung cancer is likely to be diagnosed before COPD.

Although further research is needed to add evidence in this area, we conclude that our real-life data from UK primary care support the hypothesis that COPD is associated with lung cancer incidence.

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Conflict of interest statement

Victor A Kiri and Joan B Soriano are former employees of GlaxoSmithKline R&D. George T Visick is currently employed by GlaxoSmithKline R&D. Leonardo M Fabbri has served as consultant to GlaxoSmithKline, Altana Pharma, AstraZeneca, Boehringer Ingelheim, Chiesi Farmaceutici, Merck Sharp & Dohme, Novartis, Roche and Pfizer. There is no other conflict of interest in this study.

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