Eur Respir J 2009; 34: 380–386
DOI: 10.1183/09031936.00144208

COPD prevalence is increased in lung cancer, independent of age, sex and smoking history

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ABSTRACT: Chronic obstructive pulmonary disease (COPD) is a common comorbid disease in lung cancer, estimated to affect 40–70% of lung cancer patients, depending on diagnostic criteria. As smoking exposure is found in 85–90% of those diagnosed with either COPD or lung cancer, coexisting disease could merely reflect a shared smoking exposure. Potential confounding by age, sex and pack-yr smoking history, and/or by the possible effects of lung cancer on spirometry, may result in over-diagnosis of COPD prevalence.

In the present study, the prevalence of COPD (pre-bronchodilator Global Initiative for Chronic Obstructive Lung Disease 2+ criteria) in patients diagnosed with lung cancer was 50% compared with 8% in a randomly recruited community control group, matched for age, sex and pack-yr smoking exposure (n=602, odds ratio 11.6; p<0.0001).

In a subgroup analysis of those with lung cancer and lung function measured prior to the diagnosis of lung cancer (n=127), we found a nonsignificant increase in COPD prevalence following diagnosis (56–61%; p=0.45). After controlling for important variables, the prevalence of COPD in newly diagnosed lung cancer cases was six-fold greater than in matched smokers; this is much greater than previously reported.

We conclude that COPD is both a common and important independent risk factor for lung cancer.

KEYWORDS: Chronic obstructive pulmonary disease, epidemiology, lung cancer, risk, spirometry

As only 10–15% of chronic smokers get lung cancer [1], host susceptibility factors have been implicated. Age, smoking history, family history and impaired lung function have been identified as key risk factors [2]. The question that then arises is: does the association between chronic obstructive pulmonary disease (COPD) and lung cancer come down to more than a shared smoking history?

Cross-sectional studies show that the prevalence of COPD is 40–70% of those diagnosed with lung cancer [3, 4], although prevalence is highly dependent on diagnostic criteria, age, sex and smoking exposure [5]. As none of these studies compared the prevalence of COPD in their lung cancer cohorts with a smoking cohort matched for these variables, the significance of this finding is uncertain. Moreover, none of these studies considered that lung cancer may itself cause an obstructive effect on spirometry. It is possible that potential confounding by age, sex and pack-yr smoking history on COPD prevalence, and/or the possible effects of lung cancer *per se* on spirometry, could result in over-diagnosis of COPD and a falsely increased association between COPD and lung cancer.

An alternative explanation is that COPD is independently and closely related to lung cancer [6] and that these diseases even share underlying host susceptibility factors [7, 8]. This is clinically important for three reasons. First, an exaggerated or maladaptive response to smoking (or other aero-pollutant), *i.e.* induced airway inflammation, could be the basis of this susceptibility [8] and the target for future preventive drug therapies [9]. Evidence to support this proposition comes from recently reported genetic studies showing that both COPD [10] and lung cancer [11, 12] were associated with a genetic variant in the α5 subunit of the nicotinic acetylcholine receptor gene, previously implicated in smoking-induced lung inflammation [9]. Secondly, risk assessment tools designed to identify those at the greatest risk of lung cancer who may benefit from preventive strategies may incorporate these genetic variants, along with a history of COPD

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Received:
Sept 21 2008
Accepted after revision:
Jan 10 2009
First published online:
Feb 05 2009

European Respiratory Journal
Print ISSN 0903-1936
Online ISSN 1399-3003

[13]. Thirdly, the diagnosis of COPD should alert patients to their elevated risk of lung cancer [14], much as elevated blood pressure does for the risk of stroke. This increased risk is independent of smoking status [15] and may have utility in prompting high-risk people to present early with new symptoms suggestive of lung cancer [16] or be a selected group for future lung cancer screening programmes. With these observations in mind, we undertook a simple cross-sectional study to ascertain the prevalence of COPD in recently diagnosed lung cancer cases, to determine the effect of the cancer on spirometry and to establish to what degree (if any) COPD is found more often in lung cancer cases compared with an appropriately matched control group randomly recruited from the community.

MATERIALS AND METHODS

Study subjects

Patients with lung cancer (n=446) were consecutively recruited between 2004 and 2007 following referral to a specialist lung cancer clinic at a local tertiary hospital (Green Lane Clinical Centre, Auckland, New Zealand). These patients were >40 yrs of age, of Caucasian ancestry (all four grandparents of Caucasian descent) and the diagnosis was confirmed through histological or cytological specimens in 95% of cases. Nonsmokers with lung cancer were excluded from this study and only those cases of primary lung cancer with the following pathological diagnosis were included: adenocarcinoma, squamous cell cancer, small cell cancer and nonsmall cell cancer (generally large cell or bronchoalveolar subtypes). Spirometry in the lung cancer cases was performed using American Thoracic Society (ATS) criteria within 3 months of lung cancer diagnosis, prior to surgery and in the absence of pleural effusions or lung collapse (partial or complete) on plain chest radiographs. Spirometry was performed after withholding short- and long-acting bronchodilators for a minimum 4 and 12 h, respectively. Among the lung cancer cases, we identified those with previous lung function testing, which was carried out on average 2 yrs prior to diagnosis (range 1–5 yrs). This was performed by the hospital lung function laboratory using ATS criteria. In a subgroup that underwent surgery for their lung cancer, we obtained lung function ⩾6 weeks after lobectomy. Control subjects were recruited from the same city suburbs from which the lung cancer cases came, during the years 2002–2005. Subjects were recruited through a random sample from the Auckland electoral rolls (response rate of 60%) [17]. Subjects completed an investigator-administered questionnaire that covered details of ethnicity, smoking history and previous medical history. We selected those respondents between the ages of 40 and 75 yrs, with self-declared European ancestry and a minimum 10 pack-yr smoking history (n=654). Matching of the lung cancer cases with controls from the community-based survey was done by our biostatistician (G.D. Gamble) using the following parameters, matching one for one for each of the following: age at recruitment within 5 yrs, smoking history at recruitment within 5 pack-yrs and matching of sex. All participants gave written informed consent and the study was approved by the local ethics committee (Auckland Ethics Committee, Auckland, New Zealand). We used pre-bronchodilator spirometry and subjects were classified as having COPD according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria 2 or more [5, 18].

Statistical analysis

Patient characteristics in the cases and controls were compared by unpaired t-tests for continuous variables and a Chi-squared test for discrete variables (Mantel–Haenszel odds ratio).

RESULTS

Table 1 summarises the clinical characteristics of our unmatched and matched lung cancer and community-based smoking controls. From a total cohort of 654 community-based randomly selected smokers aged 40–75 yrs, we identified a subgroup of 301 subjects that were closely matched one for one with the lung cancer cases. From the tertiary hospital clinic, we identified 446 lung cancer cases of Caucasian ancestry. For the community-based smoking controls, apart from age and pack-yr smoking history (where the total group (unmatched n=654) is younger and smoked less than the matched subgroup (n=301)), the smoking control subgroup is very similar in baseline characteristics to the total group. Similarly for the lung cancer cases, apart from age and pack-yr smoking history (where the total (unmatched) group is older and smoked more than the matched subgroup), the lung cancer subgroup (n=301) is very similar in baseline characteristics to the total group (n=446) recruited from the clinic. In the matched comparison, weight was higher among controls ($p<0.001$) and current smoking less among controls ($p<0.001$) when compared with lung cancer cases (table 1). In contrast, lung function and prevalence of COPD were significantly different in the matched comparison (table 1). The demographic variables, staging and histological subtypes of the lung cancer cases in this study (tables 1 and 2) are comparable to a large series published from a cohort in the USA [19], suggesting that our lung cancer cohort is representative (histology: 17% small cell, 10% nonsmall cell, 43% adenocarcinoma, 24% squamous cell and 5% unknown histology; staging: 29% stage 1, 10% stage 2, 31% stage 3 and 30% stage 4).

On comparing lung function (table 1), we found that the lung cancer cases had consistently greater airflow limitation, regardless of COPD severity, than the matched community-based smokers. Specifically, the forced expiratory volume in 1 s (FEV_1), FEV_1 % predicted and FEV_1/forced vital capacity (FVC) ratio were lower in the lung cancer cases compared with controls. More importantly, the prevalence of COPD (pre-bronchodilator GOLD 2+ criteria) was 50% in the matched lung cancer cases compared with 8% in the matched smoking controls (n=602; OR 11.6; $p<0.0001$) corresponding to a six-fold greater prevalence. This prevalence is only slightly different to that seen in the unmatched cohorts. Figure 1 shows the distribution of FEV_1 % pred in our lung cancer cases (n=301) compared with control smokers in a local population matched for age, ethnicity and smoking exposure (n=301). Figure 2 shows the estimated proportion of lung cancer cases from smokers with COPD compared with those with normal or near normal lung function based on a GOLD 2+ prevalence of 50% among those diagnosed with lung cancer. GOLD 2+ criteria was chosen to define COPD to 1) minimise potential over-diagnosis of COPD in these older cohorts (mean age 64–65 yrs), in which low FEV_1/FVC ratio (*i.e.* GOLD 1+) is

TABLE 1 Summary of characteristics of the lung cancer cases and control smokers before and after matching

Parameter	Unmatched cohorts		Matched cohorts		p-value#
	Control smokers	Lung cancer	Control smokers	Lung cancer	
Subjects n	654	446	301	301	
Males %	57	53	53	53	
Age yrs	59±10	69±10	64±9	65±9	0.23
Height cm	170±0.09	167±0.08	168±0.09	168±0.08	0.58
Weight kg	80±16	69±15	78±15	71±16	<0.001
Smoking history					
Age started smoking yrs	18±4	17±4	18±4	18±4	0.62
Cigarettes·day^{-1}	17±9	20±10	20±7	19±9	0.33
Current smokers %	24	35	22	39	<0.001
Pack-yrs	35±20	41±25	38±18	38±18	0.93
Lung function					
FEV_1 L	2.84±0.82	1.86±0.69	2.56±0.80	1.90±0.69	<0.001
FEV_1 % pred	97±18	73±23	96±20	71±23	<0.001
FEV_1/FVC %	81±9	64±13	80±10	64±13	<0.001
Prevalence of COPD %					
GOLD 1+	10	60	15	65	<0.001
GOLD 2+	6	51	8	50	<0.001
GOLD 3+	1.2	14	1.3	15	<0.001
History of comorbidities %					
Chronic bronchitis	5	18	6	16	<0.001
Asthma	12	12	11	13	0.45

Data are presented as mean±SD, unless otherwise stated. FEV_1: forced expiratory volume in 1 s; % pred: % predicted; FVC: forced vital capacity; COPD: chronic obstructive pulmonary disease; GOLD: Global Initiative for Chronic Obstructive Lung Disease. #: comparison for matched cohorts only.

commonly seen [18], and 2) best reflect older definitions of COPD (European Respiratory Society and ATS) [5]. The prevalence of restrictive lung function (FEV_1/FVC >70% and FVC <80%) was comparable in the cases and controls (~12%) but may in part reflect differences in body mass index (BMI) between the cases and controls [18, 20]. No relationship with lung function (or COPD prevalence) was seen after subgrouping lung cancer cases according to staging although COPD prevalence was slightly higher in small cell and squamous cell lung cancers (table 2).

In a subgroup analysis of inoperable lung cancer cases (n=127), we identified lung cancer cases who had already undergone lung function testing on average 21 months (range 1–5 yrs) prior to lung cancer diagnosis. Although spirometry was slightly reduced at the time of diagnosis (table 3), we found the prevalence of COPD (as defined) only increased from 56% to 61% (p=0.45). The higher frequency of COPD in this subgroup likely reflects the greater impairment of lung function and associated inoperability.

In a second subgroup analysis of operable lung cancer cases (n=100), we identified lung cancer cases who had undergone lobectomy for their lung cancer and had repeat lung function testing on average 23 months (range 1–5 yrs) after surgery. This group was comparable to the larger lung cancer cohorts: 51% male, mean age 68 yrs, mean smoking history 37 pack-yrs, mean height 167 cm and mean weight 72 kg. In this subgroup we found post-operative lung function was reduced (table 3) and the prevalence of COPD (as defined previously) increased from 44% to 60% (p=0.02).

DISCUSSION

In the present study, we found the prevalence of COPD (pre-bronchodilator GOLD 2+) to be 50% in 301 lung cancer cases and 8% in our matched sample of community-based smoking controls with no lung cancer. In a subgroup analysis of lung cancer cases, in whom spirometry had been carried out prior to and after diagnosis (n=127), we found a small and nonsignificant increase in the prevalence of COPD following lung cancer diagnosis (56% and 61%, respectively; p=0.45). The 8% prevalence of COPD in the community-based smoking controls reported here is consistent with recently published prevalence studies worldwide [5]. We show that the prevalence of COPD was more than six-fold greater in the lung cancer cohort compared with matched smoking controls and that this did not result from over-diagnosis. We believe this may be the first case–control study of COPD prevalence in lung cancer where controls were carefully matched and the effects of lung cancer on spirometry was examined.

A number of studies have reported the results of their spirometry in newly diagnosed lung cancer [3, 4]. Although these studies use different spirometric criteria, they show that approximately 40–70% of lung cancer cases have coexisting COPD. Although our study showed a comparable COPD prevalence of 50%, these are all cross-sectional studies. In a prospective study, baseline spirometry was carried out and

TABLE 2 Lung function and chronic obstructive pulmonary disease (COPD) prevalence according to stage and histology in the lung cancer cohort[#]

Lung cancer histology[¶]	Subjects n	Staging[+]	Spirometry				COPD prevalence GOLD 2+ %
			FEV1 L	FEV1 % pred	FVC L	FEV1/FVC %	
Small cell[§]	78		1.88±0.46	72±17	2.95±0.71	64±7	53
	26	Limited	1.81±0.63	72±19	2.86±0.77	63±12	50
	52	Extensive	1.92±0.44	73±17	3.00±0.71	64±7	54
Nonsmall cell[f]	100	Stage 1	1.89±0.72	78±27	2.87±0.83	66±15	46
	34	Stage 2	1.77±0.43	71±19	2.68±0.71	67±13	42
	107	Stage 3	2.11±0.33	76±10	3.23±0.52	65±14	46
	103	Stage 4	1.93±0.87	70±25	2.97±0.67	65±11	48
Histological subtype							
Adenocarcinoma	191		1.96±0.65	77±26	2.96±0.44	66±13	45
Squamous	108		1.85±0.29	70±22	2.93±0.47	63±12	51
Nonsmall	45		1.78±0.55	71±19	2.89±0.87	62±11	47

Data are presented as mean±SD, unless otherwise stated. FEV1: forced expiratory volume in 1 s; % pred: % predicted; FVC: forced vital capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease. [#]: n=446; [¶]: histology not available in 5% of all lung cancer cases; [+]: data for accurate staging was available in 85% of nonsmall cell lung cancer cases; [§]: total n=78, 17%; [f]: total n=344, 77%.

incident lung cancer cases were identified over a 20-yr follow-up period [21]. In the present study, 48% of those diagnosed with lung cancer had pre-existing COPD (based on the similar spirometric criteria) on baseline spirometry. We assume that had spirometry been done closer to the time of diagnosis, the prevalence of COPD would have been somewhat higher. These findings support those of a recently reported prospective study by WILSON *et al.* [22], in which lung cancer (n=99) was diagnosed following yearly computed tomography (CT) screening. In the WILSON *et al.* [22] study, the prevalence of COPD according to GOLD 1+, 2+ and 3+ criteria was 67%, 51% and 15%, respectively, almost identical to those reported here. As expected, the prevalence of COPD (GOLD 2+) in that study was 29% in the nonrandomised ''noncases'' who were younger and had smoked less. In contrast to the current study, emphysema was systematically scored for severity by WILSON *et al.* [22] and, consistent with others, shown to be independently associated with lung cancer. We found ~12% of our lung cancer cases had restrictive lung function comparable to other studies [21]. However, we did not find any difference in restrictive lung function between cases and controls, although differences in BMI may be, in part, obscuring any difference [18, 20].

Although the above studies are in agreement, and confirm that a half or more of lung cancer cases have coexisting COPD, it is

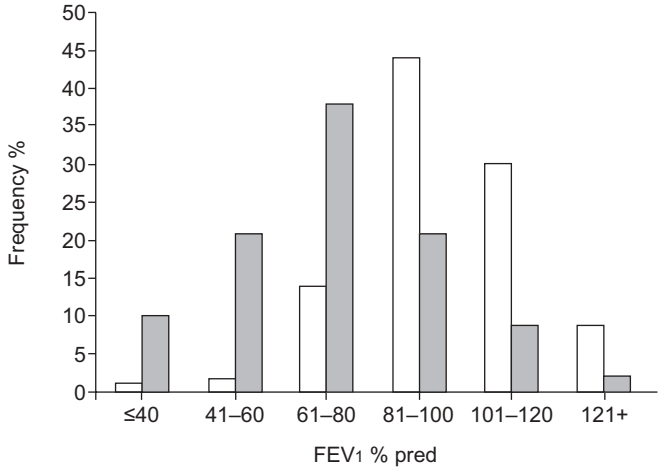

FIGURE 1. Frequency distribution of forced expiratory volume in 1 s (FEV1) % predicted in smoking controls (□) and lung cancer cases (■) (n=602) matched for age, sex and smoking history.

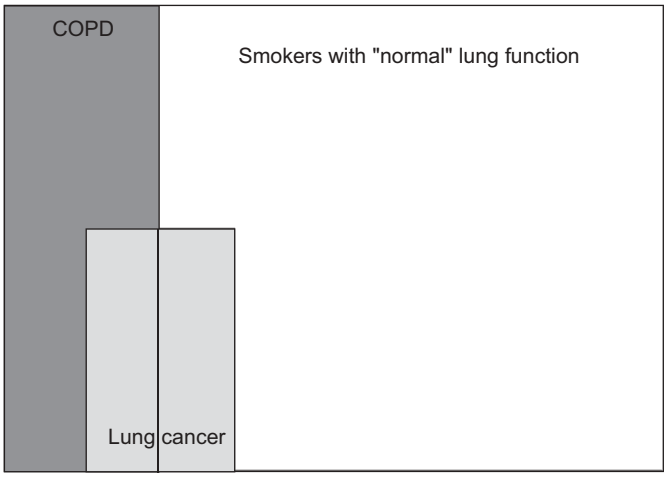

FIGURE 2. Relationship between lifetime risk of chronic obstructive pulmonary disease (COPD; Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2+) and lung cancer in chronic smokers (n=100). Assuming ~20 (20%) out of 100 of smokers get COPD (GOLD 2+; ■) and ~10 (10%) out of 100 of smokers get lung cancer (■) then if 50% of the latter have pre-existing COPD then five (25%) out of 20 with COPD get lung cancer while five (6%) out of 80 with ''normal'' lung function get lung cancer.

TABLE 3 Spirometry and chronic obstructive pulmonary disease (COPD) prevalence in lung cancer cases before and after diagnosis and lobectomy for lung cancer

Lung function	Lung cancer diagnosis[#]			Lobectomy for lung cancer[¶]		
	Before	After	Mean difference	Before	After	Mean difference
FEV_1 L	1.73±0.71	1.60±0.69	-0.123	2.05±0.80	1.67±0.69	-0.380
FEV_1 % pred	68±18	65±23	-3	81±20	69±23	-13
FVC L	2.71±0.73	2.79±0.65	0.06	3.11±0.82	2.77±0.77	-0.340
FEV_1/FVC %	63±9	58±13	-5	66±10	61±13	-5
Spirometric COPD GOLD 2+ %	56	61[+]		44	60[§]	

Data are presented as mean±SD, unless otherwise stated. FEV_1: forced expiratory volume in 1 s; % pred: % predicted; FVC: forced vital capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease. [#]: n=127; [¶]: n=100; [+] p=0.45; [§]: p=0.02.

not clear whether (or by how much) the presence of lung cancer may alter lung function at the time of diagnosis of lung cancer. The question then arises: Does the presence of lung cancer itself alter the spirometry and cause an over-estimate of COPD prevalence? To the best of our knowledge, no studies have attempted to assess the change in lung function before and after lung cancer diagnosis. In a subgroup analysis of lung cancer cases (n=127), we have identified patients with lung function tests prior to their diagnosis of lung cancer (mean 21 months). These patients had undergone spirometry primarily for symptoms of breathlessness. In comparing lung function before and after diagnosis of lung cancer, we found only a small reduction in lung function (table 3) and a nonsignificant increase in COPD prevalence from 56% to 61% in this cohort (p=0.45). Lung function was measured on average 21 months (range 1–5 yrs) before the diagnosis of lung cancer. This observation suggests that over-diagnosis of COPD resulting from lung cancer *per se* is only modest relative to the prevalence observed in a matched smoking control cohort. Support for this conclusion comes from the study of WILSON *et al.* [22], where early stage lung cancers were diagnosed prospectively during CT screening and yet COPD prevalence at baseline was very comparable to prevalence reported in the present study (*i.e.* no suggestion of over-diagnosis of COPD due to the presence of more advanced stages of lung cancer itself). Further support for this comes from the observation that lung function (or COPD prevalence) was not significantly affected by lung cancer stage (table 2). In contrast, the effect of surgery to resect the tumour might alter the prevalence of COPD. Studies examining lung function after lobectomy suggest that lung function is only mildly affected [23, 24]. The results from our study are very similar to those from WIN *et al.* [23], who in a similarly sized study reported pre-operative FEV_1 of ~2 L, dropping on average 600 mL, compared with 400 mL in our study (table 3). Not surprisingly, this results in a significant increase in the prevalence of COPD from 44% to 60% (p=0.02) in the group who have had surgery.

The confirmation that ~50% of lung cancer cases have co-existing moderate-to-severe (GOLD 2+) COPD has a number of implications. First, it suggests that a disproportionate number of lung cancer cases occur in smokers with pre-existing COPD compared with those with normal (or near normal) lung function (fig. 2). Prospective studies suggest that 20% of smokers get COPD [25] and prevalence studies suggest ~10% of the smoking population, in a comparable age band to those with lung cancer (40–75 yrs), have COPD [5]. On the basis that ~50% of lung cancer cases have co-existing moderate to severe COPD and, conservatively, 10% of chronic smokers get lung cancer, then a disproportionate number of lung cancer cases stem from patients with pre-existing COPD (one in four or 25% get lung cancer) compared with those smokers with ''normal'' lung function (one in 16 or 6% get lung cancer; fig. 2). We suggest that the risk of lung cancer among those with COPD may be closer to six-fold higher, much greater than the estimated two-fold increased risk previously associated with COPD [26]. Our results are consistent with those of prospective studies which also show, after adjustment for smoking, that COPD (based on GOLD 2+) confers up to a six-fold greater risk for lung cancer when compared with smokers with truly normal lung function [6, 21, 27]. These studies suggest that impaired lung function (based on reduced FEV_1) is more important than age or smoking exposure (measured as pack-yrs) [15, 27]. In a small CT screening study from Spain, the vast majority of lung cancer cases (20 (87%) out of 23) had either spirometric evidence of COPD (16 (69%) out of 23 with GOLD 1+) or radiological evidence of emphysema of variable severity (17 (74%) out of 23) [28]. Furthermore, mortality studies of patients with COPD suggest 20–30% die from lung cancer [29]. Such a strong association suggests COPD should be considered the most important underlying risk factor for lung cancer, greater than that attributed to smoking dose or age. Such a view is supported by a recently published study showing that even in nonsmokers, impaired lung function is associated with an increased risk of lung cancer [15]. Collectively, these studies show that not only is COPD (or airflow limitation) closely associated with lung cancer, independent of smoking exposure dose and age, but the magnitude of the association is much greater than generally appreciated.

Certainly if obstructive pulmonary function carries up to a six-fold increase in risk for lung cancer, it is much greater than that seen for other clinical variables, such as elevated blood pressure or cholesterol (each conferring a two-fold increased risk for coronary artery disease) that are routinely measured

for risk assessment and targeted cardiovascular prevention. This argues strongly for the routine use of spirometry in smokers to identify those with COPD and those with a significantly elevated risk for lung cancer, both of which have previously been shown to assist in smoking cessation [30–32].

A second implication from this strong association between COPD and lung cancer is the possibility that both diseases result from shared pathogenic mechanisms. It has been hypothesised that COPD is due to an inherent susceptibility (exaggerated or maladaptive response) to chronic inflammation [7–10, 14]. Interestingly, smoking-induced airway inflammation typically persists in those smokers with COPD for many years after quitting smoking [33]. This persistent inflammation may, in part, explain why ~50% of lung cancer cases are found in ex-smokers [3, 10, 19]. We propose that susceptibility to lung cancer and COPD results from overlapping or shared genetic effects [7–10, 13, 14], most likely expressed through smoking-induced inflammation. Support for this hypothesis comes from recently reported genetic association studies identifying a genetic variant in the α5 subunit of the nicotinic acetylcholine receptor gene, which has been implicated in smoking-induced lung inflammation [9], with both COPD [10] and lung cancer [11, 12]. Assuming this is true, and that other genetic variants confer susceptibility to both lung cancer and COPD [7], then common pathological pathways could be targeted for preventive treatment.

A third implication of the apparently close relationship between COPD and lung cancer is in the development of risk tools designed to identify those at greatest risk of lung cancer. As is the case for risk tools for other common conditions such as breast cancer (Gail Score for breast cancer) and coronary artery disease (Framingham score for myocardial infarction), increasing age is central to the assessment of the risk of lung cancer [13, 34]. Other variables used in lung cancer risk tools include smoking history, asbestos exposure and the presence of pre-existing lung disease, notably COPD [10, 13, 34]. The results of our study and the other studies discussed above emphasise the importance of COPD as an important and independent risk variable in the risk assessment of lung cancer. We believe that, just as it is important to measure and document blood pressure (for risk of future stroke), bone mineral density (for risk of future fractures) or BMI (for risk of future diabetes), lung function should be measured and recorded for assessing the risk of future lung cancer [10, 13–15, 34]. The assessment of lung cancer risk and the utility of measuring lung function have potential clinical benefits in smoking cessation [30–32] and targeted CT screening [35]. There may also be utility in the early diagnosis of lung cancer where delays in the diagnosis [16], tumour size and mortality are closely related [36].

In summary, the close relationship between COPD and lung cancer identified in this and other studies is not just about a shared smoking exposure, but likely to reflect in part, a shared genetic susceptibility to chronic smoking-induced inflammation. This association has clinical implications for the wider use of spirometry for the early identification of those at the greatest risk of lung cancer [10, 13–15, 34] and those who will have the most to gain from targeted smoking cessation and early diagnostic work-up for lung cancer [35].

STATEMENT OF INTEREST

None declared.

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