ERJ Express. Published on February 5, 2009 as doi: 10.1183/09031936.00144208

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

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Short title: **Prevalence of COPD in lung cancer.**

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Abstract

Chronic obstructive pulmonary disease (COPD) is a common co-morbid disease in lung cancer, estimated to affect between 40-70% depending on diagnostic criteria. As smoking exposure is found in 85-90% of those diagnosed with either COPD or lung cancer, co-existing disease could merely reflect a shared smoking exposure. Potential confounding by age, gender and pack year history and/or the possible effects of lung cancer on spirometry, may result in "over-diagnosis" of COPD prevalence. In this study the prevalence of COPD (pre-bronchodilator GOLD 2+ criteria) in patients diagnosed with lung cancer was 50% compared to 8% in a randomly recruited community control group, matched for age, gender, and pack year exposure (n=602, OR=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 non-significant increase in COPD prevalence following diagnosis (56% to 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 and this is much greater than previously reported. We conclude that COPD is both a common and important independent risk factor for lung cancer.

Introduction

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 COPD and lung cancer come down to more than a shared smoking history?

Cross sectional studies show that the prevalence of COPD is between 40-70% of those diagnosed with lung cancer [3,4] although prevalence is highly dependent on diagnostic criteria, age, gender 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 the lung cancer may itself cause an obstructive effect on spirometry. It is possible that potential confounding by age, gender and pack year 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 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) 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 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]. Second, risk assessment tools designed to identify those at greatest risk of lung cancer who may benefit from preventive strategies may incorporate these genetic variants along with a history of COPD [13]. Third, the diagnosis of COPD should alert patients to their elevated risk of lung cancer [14] much as elevated blood pressure does for 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 to an appropriately matched control group randomly recruited from the community.

Methods

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. These patients were over 40 yrs of age, of Caucasian ancestry (all 4 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 non-small 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 following lung cancer diagnosis, and prior to surgery and in the absence of pleural effusions or lung collapse (partial or complete) on plain chest x-ray. Spirometry was performed after with-holding short and long acting bronchodilators for a minimum 4 and 12 hrs respectively. Among the lung cancer cases we identified those with previous lung function testing on average within 2 years prior to diagnosis (range 1-5 years). This was performed by the hospital lung function laboratory using ATS criteria. In a subgroup who underwent surgery for their lung cancer we obtained lung function 6 or more 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 old, self declared European ancestry with a minimum 10 pack year smoking history (n=654). Matching of the lung cancer cases with controls from the community based survey was done by our biostatistician (GDG) using the following parameters: matching one for one for each of the following; age at recruitment within 5 years, pack years at recruitment within 5 pack years and matching of gender. All participants gave written informed consent and the study was approved by the local Ethics Committee. We used pre-bronchodilator spirometry and subjects were

classified as having COPD according to Global Initiative for 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 chi-square test for discrete variables (Mantel-Haenszel OR=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, we identified a subgroup of 301 that were closely matched one for one to 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 year 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 base line characteristics to the total group. Similarly for the lung cancer cases, apart from age and pack year 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 base line characteristics to the total group (n=446) recruited from clinic. In the matched comparison, weight was higher among controls ($P<0.001$) and current smoking less among controls ($P<0.001$) when compared to cases (Table 1). By 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 US cohort [19] suggesting that our lung cancer cohort is representative (Histology:17% Small cell, 10% Non-small 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 FEV_1, FEV_1 %predicted and FEV_1/FVC ratio were lower in the lung cancer cases compared to controls. More importantly, the prevalence of COPD (pre-bronchodilator GOLD 2+ criteria) was 50% in the matched lung cancer cases compared to 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 % predicted in our lung cancer cases (n=301) compared to 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 to 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 (a) to minimize potential over-diagnosis of COPD in these older cohorts (mean age 64-65 years old) where low FEV_1/FVC ratio (ie GOLD 1+) is commonly seen [18], and (b) best reflects older definitions of COPD (ERS 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 BMI between the cases and controls [18,20]. No relationship with lung function (or COPD prevalence) was seen after sub-grouping 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 years) 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 on average 23 months (range 1-5 years) after surgery. This group was comparable to the larger lung cancer cohorts: 51% male, mean age=68 yrs, mean pack yrs=37, mean height=167cm and mean weight=72kg. In this subgroup we found post-operative lung function was reduced (Table 3) and the prevalence of COPD (as defined above) increased from 44% to 60% (p=0.02).

Discussion

In our 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, where spirometry had been done prior to and after diagnosis (n=127), we found a small and non-significant 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 world-wide [5]. We show that the prevalence of COPD was more than six fold greater in the lung cancer cohort compared to matched smoking controls and that this did not result from over-diagnosis. We believe this maybe 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 co-existing COPD. Although our study showed a comparable COPD prevalence of 50%, these are all cross sectional studies. In a prospective study, baseline spirometry was done and incident lung cancer cases identified over a 20 year follow up period [21]. In this 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. where lung cancer (n=99) was diagnosed following yearly CT screening [22]. In the Wilson 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 non-randomised "noncases" who were younger and had smoked less. In contrast to the current study, emphysema was systematically scored for severity by Wilson et al. and, consistent with others, shown to be independently associated with lung cancer. We found about 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 co-existing COPD, it is not clear whether (or by how much) the presence of lung cancer may alter the lung function at the time of diagnosis of the 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 non-significant increase in COPD prevalence from 56% to 61% in this cohort (p=0.45). Lung function was measured on average 21 months before the diagnosis of lung cancer (range 1-5 yrs). 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., where early stage lung cancers were diagnosed prospectively during CT screening [22] and yet COPD prevalence at "baseline" was very comparable to prevalence reported in this study (ie. 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 affect 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 approximately 2 litres dropping on average 600ml compared with 400ml 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 approximately 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 to those with normal (or near normal) lung function (Figure 2). Prospective studies suggest that 20% of smokers get COPD [25] and prevalence studies suggest about 10% of smoking populations, in a comparable age band to those with lung cancer (40-75 years) have COPD [5]. On the basis that approximately 50% of lung cancer cases have co-existing moderate-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 (1 in 4 or 25% get lung cancer) compared to those smokers with "normal" lung function (1 in 16 or 6% get lung cancer) (see Figure 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 2 fold increased risk previously associated with COPD [26]. Our results are consistent with that of prospective studies which also show, after adjustment for smoking, COPD (based on GOLD 2+) confers up to a 6 fold greater risk for lung cancer when compared to 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 years)[15,27]. In a small CT screening study from Spain, the vast majority of lung cancer cases (87% or 20/23) had either spirometric evidence of COPD (16/23 or 69% with GOLD 1+) or radiological evidence of emphysema of variable severity (17/23 or 74%) [28]. Furthermore, mortality studies of patient with COPD suggest between 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 non-smokers', 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 6 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 2 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 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 hypothesized that COPD is due to an inherent susceptibility (exaggerated or maladaptive response) to chronic inflammation [7-10, 14]. Interestingly, smoking-induced airways inflammation typically persists in those smokers with COPD for many years after quitting smoking [33]. This persistent inflammation may, in part, explain why approximately 50% of lung cancer cases are found in ex-smokers [3,10,19]. We propose that susceptibility to lung cancer and COPD results from over-lapping 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, that 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 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 emphasize 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 body mass index (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 benefit in smoking cessation [30-32] and targeted CT screening [35]. There may also be utility in early diagnosis of lung cancer where delays in diagnosis [16], tumor 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 to identify early those at greatest

risk of lung cancer [10,13-15,34] and who will have the most to gain from targeted smoking cessation and early diagnostic work up for lung cancer [35].

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Table 1. Summary of characteristics of the Lung cancer cases and Control smokers before and after matching.

	Unmatched cohorts		***Matched cohorts***		
Parameter Mean (1 SD)	***Control smokers N=654***	***Lung cancer N=446***	***Control smokers N=301***	***Lung cancer N=301***	***Differences* p***
% male	*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	*18 (4)*	*17(4)*	*18 (4)*	*18 (4)*	*0.62*
Cigarettes/day	*17 (9)*	*20 (10)*	*20 (7)*	*19 (9)*	*0.33*
Current smokers	*24%*	*35%*	*22%*	*39%*	*<0.001*
Pack years	*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 % predict	*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 co-morbidities					
Chronic bronchitis	*5%*	*18%*	*6%*	*16%*	*<0.001*
Asthma	*12%*	*12%*	*11%*	*13%*	*0.45*

** Comparison for matched cohorts only*

Table 2. Mean lung function **(1 SD)** and COPD prevalence according to stage and histology in the lung cancer cohort (n=446).

Lung Cancer histology#	Staging*	Spirometry				COPD prevalence (GOLD 2+)
		FEV_1 (L)	FEV_1 %predicted	FVC	FEV_1/FVC	
Small Cell	Limited n=26	1.81 (0.63)	72% (19%)	2.86 (0.77)	63% (12%)	50%
n=78 (17%)	Extensive n=52	1.92 (0.44)	73% (17%)	3.00 (0.71)	64% (7%)	54%
Total n=78		1.88 (0.46)	72% (17%)	2.95 (0.71)	64% (7%)	53%
Non-Small Cell						
n= 344 (77%)	Stage 1 (29%)	1.89 (0.72)	78% (27%)	2.87 (0.83)	66% (15%)	46%
	Stage 2 (10%)	1.77 (0.43)	71% (19%)	2.68 (0.71)	67% (13%)	42%
	Stage 3 (31%)	2.11 (0.33)	76% (10%)	3.23 (0.52)	65% (14%)	46%
	Stage 4 (30%)	1.93 (0.87)	70% (25%)	2.97 (0.67)	65% (11%)	48%
Histological subtype						
Adeno (n=191)	-	1.96 (0.65)	77% (26%)	2.96 (0.44)	66% (13%)	45%
Squamous (n=108)	-	1.85 (0.29)	70% (22%)	2.93 (0.47)	63% (12%)	51%
Non-small (n=45)	-	1.78 (0.55)	71%((19%)	2.89 (0.87)	62% (11%)	47%

Histology not available in 5% of all lung cancer cases. * Data for accurate staging was available in 85% of Non-Small Cell lung cancer cases.

Table 3. Mean (SD) or % differences in spirometry and COPD prevalence in lung cancer cases before and after (a) diagnosis (n=127) and (b) lobectomy for lung cancer (n=100).

	Lung cancer diagnosis (n=127)			***Lobectomy for lung cancer (n=100)***		
Lung function (1 SD)	***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 % predict	*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%#*	

*** p=0.45, #p=0.02**

Figure 1. Frequency distribution of % predicted FEV_1 in smoking controls and lung cancer cases (n=602) matched for age, gender and smoking history.

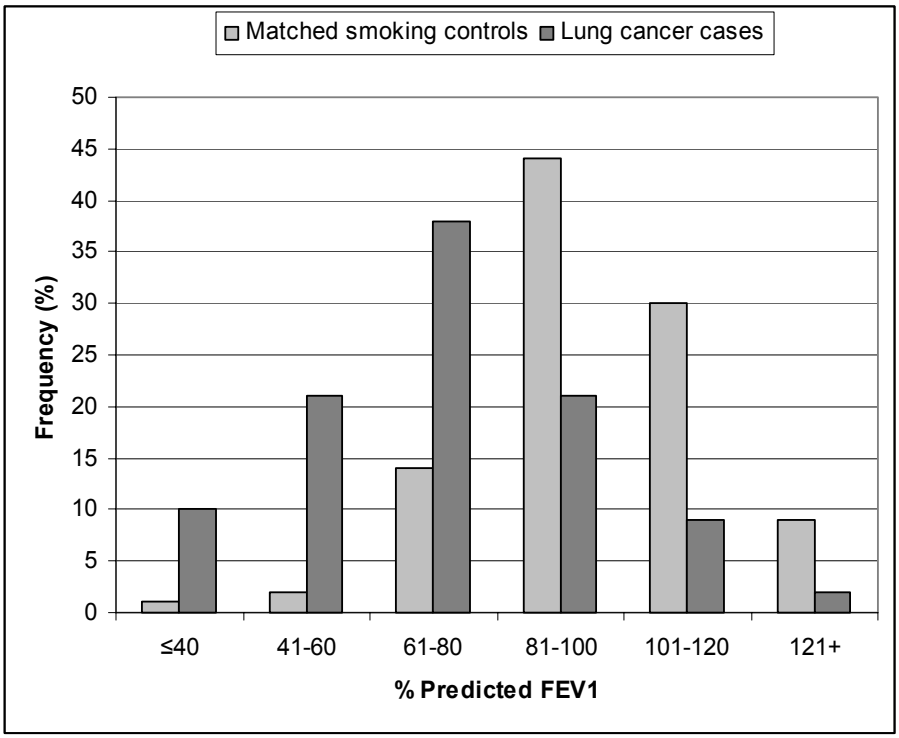
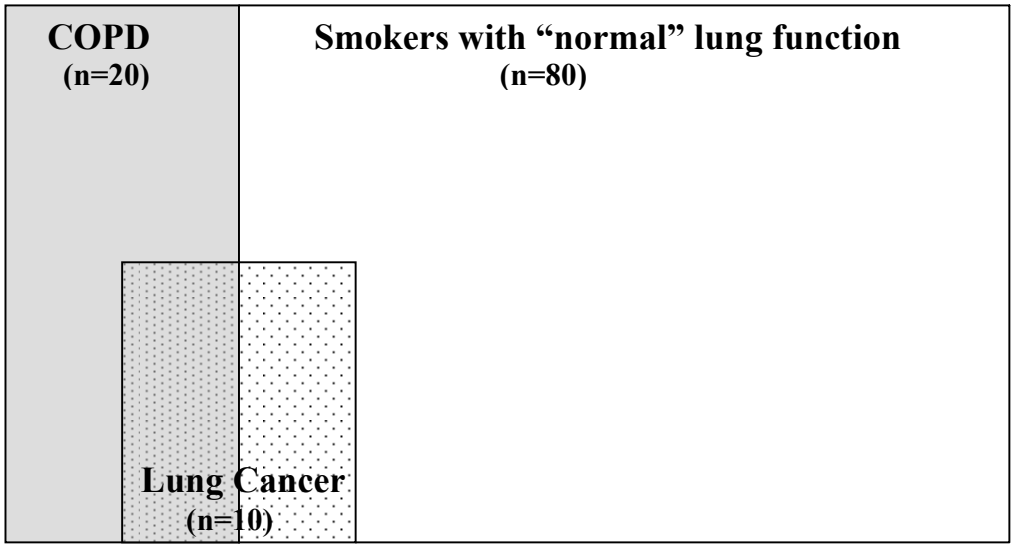


Figure 2 Relationship between lifetime risk of COPD (GOLD 2+) and lung cancer in chronic smokers (n=100).



Assuming approximately 20/100 or 20% of smokers get COPD (GOLD 2+, grey area) and approximately 10/100 or 10% of smokers get lung cancer (dotted area) then if 50% of the latter have pre-existing COPD then 5/20 (25%) with COPD get lung cancer while 5/80 (6%) with "normal" lung function get lung cancer.