Lung cancer is a major public health problem worldwide. In 2000, 328 million people died from lung cancer globally. In Europe, 266,000 men and 64,000 women died from lung cancer in 1995. In the US there were over 170,000 new cases of lung cancer and more than 160,000 deaths related to lung cancer in 2004. This makes lung cancer the leading cause of cancer deaths in both men and women. Indeed, in the US, lung cancer causes more deaths than the next three most common cancers combined (colon cancer, n = 48,100; breast cancer, n = 40,000; and prostate cancer, n = 30,200).

The leading cause of lung cancer is cigarette smoking. Other risk factors include exposures to certain occupational hazards, combustion generated carcinogens, and ambient radiation. Some have argued that reduced lung function is another important risk factor for lung cancer. However, several epidemiological questions regarding this relationship remain unanswered. Firstly, since individuals with reduced lung function frequently have a significant smoking history, it is not certain whether the relationship between lung function and lung cancer is real or simply confounded by the effects of smoking. Secondly, it is not known whether the relationship between impaired lung function and lung cancer is dose dependent or threshold dependent. Thirdly, even if there is a significant relationship between these two parameters, it is not known whether sex modifies this relationship. To address these questions we conducted a systematic review and meta-analysis of population-based studies of the relationship between lung function and lung cancer risk.

METHODS

Search for relevant studies

Using PubMed (1966–2004) and EMBASE databases, we conducted a comprehensive literature search to identify relevant studies published before January 2005 that examined the relationship between forced expiratory volume in 1 second (FEV1) and lung cancer. We used a disease specific search term (lung neoplasm*) combined with lung function specific search terms (FEV, FEV1, forced expiratory volume, lung function) in all our searches. The electronic searches were supplemented by scanning the reference lists from retrieved articles to identify additional studies that may have been missed during the initial search. We also contacted the primary authors of the study for clarification of data where necessary.

Study selection and data abstraction

The primary outcome of this systematic review was to compare the relative risk of lung cancer among subjects who had impaired lung function, as measured by FEV1, against those who had "normal" lung function at baseline assessment. To mitigate publication bias, we limited our search to studies that (1) were population based and did not select participants on the basis of disease; (2) employed a prospective design; (3) were large in size (at least 5000 participants); (4) used standardised methods for measuring FEV1; (5) adjusted for important confounders including age, sex, race, height, and smoking status; and (6) divided the cohort into quintiles. The latter criterion allowed us to determine the shape of the relationship between FEV1 and lung cancer.

From each relevant article two investigators (SW, WQG) abstracted the following information: first author, publication year, population sampled, sample size, lung cancer incidence or mortality, follow up time, age, sex, smoking history, FEV1, and other factors (table 1). Any questions or discrepancies regarding these data were resolved through iteration and consensus.
Statistical methods
Quintile 5 was defined as the group with the best FEV₁, and quintile 1 as the group with the worst FEV₁. For the primary end point we included all incident cases of lung cancer or deaths from lung cancer, whichever were reported in the original study. There were no studies in which both of these variables were reported. A weighted mean difference technique was used to pool the original data together. The weighted mean difference was derived using an inverse variance weighting method. For each outcome the heterogeneity of variance—was used to pool the results together. In the random effects model—which assigns a weight to each study—was used to pool the original data together. The weighted mean difference was derived using an inverse variance weighting method. For each outcome the heterogeneity of variance was observed (p<0.10), a random effects model—which assigns a weight to each study based on individual study variance as well as between study variance—was used to pool the results together. In the absence of significant heterogeneity a fixed effects model was used. Data analysis was conducted for men and women separately and combined. All analyses were conducted using Review Manager Version 4.2 (Revman; Cochrane Collaboration, Oxford, UK).

RESULTS
The study selection process is summarised in fig 1. The electronic literature search yielded 333 citations from PubMed and 16 from EMBASE. The abstracts of these articles were reviewed for suitability. The reasons for exclusion are summarised in fig 1. In all, we identified four studies which met the inclusion and exclusion criteria and were published in the analyses. In three of these studies we abstracted the salient data from published reports and in the fourth we used the public use data files from the National Center for Health Statistics. The relevant baseline data from each of the selected studies are summarised in table 1 and the FEV₁ data for each quintile group are summarised in table 2. In total, the analysis included 204 990 participants of whom 6185 had or died from lung cancer. The average age of the participants ranged from 42 to 47 years at baseline across the original studies. The follow up time was 9–18 years (table 1).

After adjustments for important covariates such as age, cigarette smoking, and body mass index, participants in quintile 5 (the group with the best FEV₁) had the lowest risk of lung cancer while those in quintile 1 (the group with the worst FEV₁) had the highest risk of lung cancer (table 3). Surprisingly, even those in quintiles 3 and 4, who had relatively well preserved lung function (mean FEV₁ ~80–100% of predicted), also had an increased risk of lung cancer. The relationship was particularly notable in women where those in quintiles 3 and 4 had risks of lung cancer that were 3.5 and 2.6 fold higher, respectively, than those in quintile 5.

The relationship between FEV₁ quintiles and the incidence of lung cancer in both men and women is summarised in table 3 and illustrated in fig 2. The slope of the relationship was significantly steeper in women than in men (p<0.001). Moreover, for every quintile, the relative risk of lung cancer

<table>
<thead>
<tr>
<th>Table 1 Baseline characteristics of included studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Author</td>
</tr>
<tr>
<td>--------</td>
</tr>
<tr>
<td>Hole²⁰</td>
</tr>
<tr>
<td>Koller¹²</td>
</tr>
<tr>
<td>Mannino²²</td>
</tr>
<tr>
<td>Van Dan Eden¹³</td>
</tr>
</tbody>
</table>

SD, standard deviation; FEV₁, forced expiratory volume in 1 second; NR, not reported; BMI, body mass index.

*These values represent the percentage of participants who smoked >15 cigarettes daily.

Search results N=349
PubMed: n=333
EMBASE: n=16

Not cohort based studies with over 5000 participants n=321

Studies reviewed for inclusion n=28

Did not include data based on FEV₁ n=6
Did not adjust for confounding factors n=8
Not prospective studies n=3
Did not divide participants into quintiles n=7

Studies included in analysis n=4

Figure 1 Study selection process. FEV₁, forced expiratory volume in 1 second.
was higher in women than in men. These data suggest that the effects of reduced FEV₁ are amplified in women.

In table 4 we have summarised the remaining large epidemiological studies that evaluated the relationship between FEV₁ and the risk of lung cancer. Similar to the results of the present meta-analysis, all of these studies showed that reduced FEV₁ was a significant risk factor for lung cancer. These results could not be used in the meta-analysis, however, because of the marked heterogeneity in the way in which the data were collected and reported across the studies.

DISCUSSION

This systematic review of population based studies which have examined the relationship between lung function and lung cancer has produced several interesting observations. Firstly, independent of cigarette smoking history, reduced FEV₁ increases the risk for lung cancer in the general population. Secondly, the relationship is severity dependent such that individuals with the worst lung function have the highest risk whereas those with preserved lung function have the lowest risk. Thirdly, the relationship is linear; relatively small differences in FEV₁ which are commonly considered within the normal range (for example, from 90% of predicted to 100% of predicted) increase the risk of lung cancer by 30–60%. Fourthly, the risk appears to be amplified in women.

The finding that reduced FEV₁ at baseline is significantly associated with an increased risk of lung cancer is consistent with several previous reports. Although baseline health status, degree of abnormality in lung function, and length of follow up varied considerably between the various cohorts, the associations were remarkably similar.

There are several possible explanations for a relationship between lung function and lung cancer. Firstly, the outcomes may share a causal pathway. One possible shared pathway is lung and airway inflammation which are known to correlate with the decline in lung function among smokers. Inflammation is thought to be an important mechanism responsible for the proteolytic lung destruction and small airway remodelling and narrowing which reduce lung function in smokers and in chronic obstructive pulmonary disease (COPD), and is also implicated in the decline in lung function in asthma and pulmonary fibrosis. Hence, reduced FEV₁ may be part of the process related to lung and airway inflammation. Airway inflammation may also have a major role in the pathogenesis of lung cancer. Cigarette smoke and other noxious irritants incite a vigorous inflammatory reaction in the airways leading to the recruitment and activation of pro-inflammatory cells such as...
leucocytes which, in turn, propagate the inflammatory cascade through the release of various cytokines and reactive oxidative species.27 These latter molecules can cause oxidative damage and promote DNA mutagenesis in the surrounding lung cells.28 If the rate of cell division exceeds the rate at which reactive oxidative species related DNA damage can be repaired, DNA mutagenesis may occur and the risk for cancer increases.29 Reactive oxidative species may also directly activate various oncogenes in the surrounding cells and tissues (for example, jun and fos) which may further increase the risk of lung cancer.29 Consistent with this inflammatory hypothesis for lung cancer, the incidence of lung cancer is increased in inflammatory lung conditions such as idiopathic pulmonary fibrosis,30 asbestos, and sarcoidosis.31 A corollary of the “shared pathogenesis” hypothesis is that the genes which impart risk for COPD and lung cancer may be common. For instance, individuals who have polymorphisms in genes which influence the oxidant/antioxidant balance in favour of reactive oxidative species may be susceptible to both.

A second possible explanation for the relationship is that the lung dysfunction secondarily enhances the risk of cancer. Individuals who have reduced FEV1 may have an impaired sample text...
ability to clear inhaled carcinogens from their airways. This could lead to increased contact time between carcinogens and airway epithelial cells. However, this seems unlikely because individuals in quintiles 3 and 4 had “normal” FEV₁ levels and yet had an increased risk of lung cancer.

In the present study the relationship between FEV₁ and lung cancer was modified by sex. Whether women are more susceptible to lung cancer than men is controversial. Several epidemiological studies have reported data indicating increased susceptibility for lung cancer in women compared with men. However, other studies have shown the reverse, with men being more susceptible to lung cancer than women, while other studies have demonstrated equal susceptibility. In Notwithstanding these data, there is little doubt that there are important biological and histological differences in lung cancer between women and men. For instance, in women, adenocarcinoma is by far the leading histological subtype of lung cancer whereas, in men, squamous and adenocarcinomas are equally prevalent. Interestingly, the contribution of cigarette smoking to the risk is less apparent for adenocarcinomas than for other histological subtypes. Although lung cancer is rare in lifetime non-smokers, if it develops in these individuals it is usually an adenocarcinoma. Moreover, smoking cessation rapidly reduces the risk for squamous cell carcinoma while the risk for adenocarcinomas decreases much more slowly.

In general, women have a higher frequency of GC→TA mutations and transversions in the p53 gene in resected lung tumour specimens than men, even though the level of exposure to carcinogens from cigarette smoking may be lower in women. Furthermore, higher levels of smoking related hydrophobic DNA adducts have been reported in the lung cancers and adjacent tissues in women. Female smokers also exhibit significantly higher expression levels of lung CYP1A1 than men. Increased CYP1A1 expression is important in determining individual susceptibility to lung cancer and may be a critical factor for influencing differences between sexes in levels of aromatic/hydrophobic DNA adducts in the lung. A lower DNA repair capacity in women than in men may also contribute to the variation in susceptibility between women and men.

There are several limitations to this study. Cigarette smoking is a risk factor for lung function and lung cancer and could confound the relationships observed between FEV₁ and lung cancer. However, all of the original studies included in the meta-analysis carefully controlled for the effects of cigarette smoking, making it unlikely that our results could be explained away by smoking. Nevertheless, we cannot fully discount the possibility of residual confounding by smoking. Secondly, we did not have data on the specific histological subtypes of cancer so the relationship between FEV₁ and specific histological subtypes of lung cancer remains largely unknown, although the results of a previous study suggest that adenocarcinomas are more likely to develop in those who have small decreases in FEV₁ and squamous cell carcinomas are more likely in those with severe impairment of lung function. Thirdly, publication bias is a concern. To mitigate this bias we chose only large population based studies. Since small positive studies are more likely to get published than small negative studies, by not including results from small studies the relative risk estimates of reduced FEV₁ of the current meta-analysis may be lower than those previously published. Fourthly, most of the original studies were conducted in relatively young individuals, so the findings of the present meta-analysis may not be generalisable to the older population who develop lung cancer.

Lung cancer is the most lethal cancer in the world. The only reasonable chance for cure is to uncover the disease at a localised stage. However, patients are rarely symptomatic at early stages of disease when curative resection would be possible. Most patients present at advanced stages of the disease, so screening and early diagnosis of lung cancer are therefore imperative in reducing case fatality rates. The present study demonstrates a strong inverse relationship between FEV₁ and lung cancer which applies to all levels of FEV₁. The risk increases even with a relatively modest reduction in FEV₁, especially among women. We found that women were approximately twice as likely to develop lung cancer as men for the same marginal decrements in FEV₁. The potential clinical implications for both current and former smokers, FEV₁ may provide criteria beyond age and smoking intensity to identify smokers at high risk for lung cancer; this discriminatory power of lung function testing may be important in selecting smokers for enrollment in chemoprevention and early detection trials. Furthermore, since lung cancer can occur in individuals with only small decreases in FEV₁, (especially in women), the traditional boundaries of “normal” FEV₁ may need to be modified for screening purposes.

Authors’ affiliations
S Wasswa-Kintu, W G Gan, S F P Man, P D Pare, D D Sin, Department of Medicine (Respiratory Division), University of British Columbia and The James Hogg iCAPTURE Center for Cardiovascular and Pulmonary Research, St Paul’s Hospital, Vancouver, British Columbia, Canada

DDS is supported by a Canada Research Chair (Respiration) and a Michael Smith/St Paul’s Hospital Foundation Professorship in COPD.

REFERENCES
Relationship between lung function and lung cancer


TIMP-3 promoter gene polymorphisms in BFL

Bird fanciers’ lung (BFL) is a form of hypersensitivity pneumonitis induced by inhalation of antigens from birds. Only a small percentage of bird fanciers will develop BFL, so it is likely that these patients have a certain genetic predisposition to the disease. Matrix metalloproteinases (MMP) are zinc enzymes responsible for the degradation of the extracellular matrix. The proteolytic activities of MMP are counter-regulated by tissue inhibitors of MMP (TIMP). Hill found a decreased carriership of the rare TIMP-3 −1296C and −915G promoter alleles in Mexican patients with pigeon induced BFL, suggesting a protective effect of these alleles against the development of this disease.

Only two previously published genetic association studies to date have focused on the susceptibility to BFL and both were performed in Mexican pigeon breeders. We have undertaken a study to validate the association between BFL susceptibility in Mexicans and TIMP-3 promoter polymorphisms in a group of Dutch white patients with BFL.

Forty one patients with BFL (35 keeping pigeons, 10 keeping budgerigars, 3 keeping parrots and 1 keeping canaries; 19 women and 22 men) and 335 controls were genotyped using sequence specific primers and polymerase chain reaction. The diagnosis of BFL was established in concordance with the criteria used in the Mexican study. The control group comprised healthy employees from our hospital. We did not include a group of bird fanciers without BFL since Hill did not find differences in TIMP-3 allele distributions between Mexican controls with or without exposure to birds. The Dutch population was in Hardy-Weinberg equilibrium. In contrast to the previous TIMP-3 study in Mexicans, we found 100% linkage between the −1296C and −915A alleles and between the −1296C and −915G alleles in subjects homozygous for the respective alleles. We were therefore able to deduce two haplotypes (1296A and 1296G). The TIMP-3 C’G haplotype frequency in BFL patients was significantly lower than in controls (p = 0.0183; OR 0.513 (95% CI 0.277 to 0.950; p = 0.0312); table 1).

Hill described a similar association in Mexican patients where he found a reduction of the rarer TIMP-3 alleles in Dutch patients with BFL (−1296C and −915G, −11%), comparable to the reduction found in Mexican BFL patients (−1296C, −12.6% ; −915G, −10.8%; table 1). However, there were differences between the findings of the two studies. The TIMP-3 −1296C and −915G allele frequencies in Dutch controls were significantly lower than in the Mexican controls (−1296C, p = 0.0008; −915G, p = 0.0183; table 1). A search on the National Center for Biotechnology Information website showed similar TIMP-3 −1296C frequencies in Dutch and American controls (30 mother-father-child trios from Utah with northern and/or western European ancestry; http://www.ncbi.nih.gov/SNP/snp_viewTable.cgi?pop = 1409; http://www.ncbi.nih.gov/SNP/snp_ref.cgi?rs = 9619511). BFL in Mexicans has a similarly poor prognosis to idiopathic pulmonary fibrosis, which contrasts with the more benign clinical course in Europeans. Although most patients in our study had severe symptoms at presentation with profound pulmonary function abnormalities, symptoms and pulmonary function improved in the majority of cases during follow up. Furthermore, we included an approximately equal number of male and female patients and bird fanciers who kept birds other than pigeons, while all the Mexican patients were female and kept pigeons only. Despite these genotypical and phenotypical differences, the rarer TIMP-3 promoter alleles were protective in both ethnic populations which makes an underlying functional cause of the C’G haplotype likely.

In conclusion, we found a decreased carriership of the TIMP-3 C’G haplotype in Dutch patients with BFL, indicating a protective effect against the development of this disease. Studying the influence of polymorphisms on disease susceptibility in multiple ethnically and geographically distinct disease and control populations is important. Our study is the first to confirm an association between polymorphisms and susceptibility to BFL, which adds importance to the mechanism by which the TIMP-3 variants may cause such a protective effect has yet to be determined.

The authors thank Hitlee Alpar, Jan Broess and Helga Dissel for their technical support.

References


Late CF caused by homozygous IVS8-5T CFTR polymorphism

The distribution of cystic fibrosis (CF) transmembrane conductance regulator (CFTR) genotypes is not well characterised in patients with CF diagnosed after childhood, the majority of whom are compound heterozygotes for AF508. We describe such a patient with a rare genotype more commonly associated with inherited infertility in males. A 54 year old man who had never smoked was referred with bilateral bronchiectasis and chronic sinusitis. He had no known allergy, no history of pancreatitis, and no family history of CF or consanguinity. Obstructive infertility with azoospermia had been established by spermography. The patient reported recent lower respiratory tract infections since childhood and pneumonia at the age of 45. He had undergone sinus surgery for nasal polyps.

CF was suspected. A first sweat test was positive with a chloride concentration of 65 mmol/l (normal <40 mmol/l). The patient had chronic cough productive of purulent sputum, mild dyspnoea, chronic nasal...
obstruction with nasal polyps and anosmia. His weight was 70 kg and his height 1.75 m. He had no digestive symptoms. Lung and heart auscultation was normal. A chest CT scan showed diffuse bronchiectasis predominating in the right upper and left lower lobes (fig 1). Lung function was near normal with forced expiratory volume in 1 second (FEV1) of 3.1 L (89% predicted), FEV1/forced vital capacity 0.73, total lung capacity 7 L (100% predicted), and forced expiratory flow25–75% 61% of predicted. Arterial oxygen tension was normal. Both sputum and bronchoalveolar lavage cultures were positive for mucinous Aspergillus fumigatus but no mycobacteria or fungi were found. Serological examination for Pseudomonas aeruginosa was negative. Exocrine pancreatic sufficiency was confirmed by normal elastase levels in the stools. A second sweat test was normal (25 mmol/L).

A screening test for the 22 most frequent mutations of the CFTR gene encountered in France was negative. However, mutations of the CFTR gene were confirmed by the presence of homozygosity for the 5T allele in the polythymidine tract of intron 8 (IVS8-5T) with 11 TG repeats. The M470V polymorphism was absent. Sequencing of the full CFTR gene was confirmed by the DNA sequence of the patient is indicated as “sequence”.

This patient had clinical features typical of CF involving several organs (bilateral bronchiectasis, chronic sinus disease, male infertility) together with two pathogenic CFTR gene mutations, so a diagnosis of non-classic CF can be made. The sweat test was positive on only one of two occasions, suggesting partial dysfunction of the CFTR protein.

The IVS8-5T allele is associated with poorly effective usage of the intron 8 splice acceptor site compared with the two other existing alleles (7T and 9T) and results in frequent skipping of exon 9. Patients homozygous for the IVS8-5T allele have lower than normal levels of full length CFTR messenger RNA and protein. Heterozygous IVS8-5T polymorphism is considered equivalent to a “mild” CFTR mutation. When in trans with a known CFTR mutation, the IVS8-5T allele may be responsible for congenital bilateral absence of the vas deferens or recurrent pancreatitis. It may modulate the variable expression of “mild” CFTR mutations such as when present in cis of the R117H mutation, thus causing a CF phenotype.

Compound heterozygotes with IVS8-5T and ΔF508 may present with classic or late onset CF. Whether IVS8-5T homozygosity may be sufficient by itself to cause disease has not hitherto been established. Non-classic CF was reported in a 48 year old woman homozygous for IVS8-5T, but the M470V polymorphism and TG12 repeat sequence known to modulate the disease penetrance of IVS8-5T were also present.

This observation shows that individuals homozygous for the IVS8-5T allele as the sole variation of the whole CFTR coding sequence may present as non-classic CF with sinus-pulmonary disease and male infertility. However, given the high prevalence of the IVS8-5T allele (5–10% in the general population), the expected frequency of individuals homozygous for IVS8-5T may be higher than the prevalence of CF, suggesting that other factors may contribute to the disease. The IVS8-5T allele should be included in the systematic screening for CFTR mutations in patients with suspected or confirmed CF.

V Cottin*, Y Thibout* Service de Pneumologie – Centre de Référence des Maladies Orphelines Pulmonaires, Hôpital Cardiovasculaire et Pneumologique Louis Pradel, Université Claude Bernard, Lyon, France

F Bey-Omar Laboratoire de Biochimie et Biologie Endocrinienne et Moléculaire, Hôpital Devrouex, Lyon, France

I Durieu Centre de Ressource et de Compétence sur la Mucoviscidose, Service de Médecine Interne, Centre Hospitalier Lyon-Sud, Pierre-Bénite, France

L Laoust 160 Place Charles de Gaulle, 74300 Cluses, France

Y Morel Laboratoire de Biochimie et Biologie Endocrinienne et Moléculaire, Hôpital Devrouex, Lyon, France

J-F Cordier Service de Pneumologie – Centre de Référence des Maladies Orphelines Pulmonnaires, Hôpital Cardiovasculaire et Pneumologique Louis Pradel, Université Claude Bernard, Lyon, France

Correspondence to: Dr V Cottin, Hôpital Louis Pradel, 28 Avenue Doyen Lépine, 69677 Lyon, France; vincent.cottin@chu-lyon.fr

*Both authors contributed equally to this work.

doi: 10.1136/thx.2005.048207

References

doi: 10.1136/thx.2004.037135corr1

In the paper entitled “Relationship between reduced forced expiratory volume in one second and the risk of lung cancer: a systematic review and meta-analysis” by S Wasswa-Kintu et al which appeared on pages 570–575 of the July 2005 issue of Thorax, the correct figure for the worldwide mortality from lung cancer in 2000 (mentioned in the second line of the first paragraph) is 0.85 million, not 328 million as stated in the article.