LUNG CANCER

Impaired lung function and lung cancer incidence in a cohort of Swedish construction workers

Mark P Purdue, Laura Gold, Bengt Järvholm, Michael C R Alavanja, Mary H Ward, Roel Vermeulen

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See end of article for authors' affiliations

Correspondence to: Dr M Purdue, Division of Cancer Epidemiology and Genetics, National Cancer Institute, EPS 8121, 6120 Executive Blvd, Bethesda, MD 20892-7240, USA; purduem@mail.nih.gov

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Background: Although impaired lung function in general has been associated with an increased risk of lung cancer, past studies typically have not attempted to investigate separately the obstructive and restrictive components of respiratory impairment. To deal with this question further, data from a large (n = 176 997) cohort of male Swedish construction workers, for whom spirometry measurements before follow-up were available, were analysed.

Methods: Cancer incidence for 1971–2001 was obtained through linkage with the national cancer registry. Using a modification of the Global Initiative for Chronic Obstructive Lung Disease criteria for chronic obstructive pulmonary disease (COPD), subjects were classified into five categories of lung function: normal, mild COPD, moderate COPD, severe COPD and restrictive lung disease (RLD). Rate ratios (RR) and 95% confidence intervals (CI) for lung cancer across lung function categories were calculated using Poisson regression, adjusted for age and smoking. Other end points (histological types of lung cancer, non-lung tobacco-related cancers, other cancers, total mortality) were also investigated.

Results: 834 incident cases of lung cancer were identified. Increased rates of lung cancer were observed for both COPD (mild: RR 1.5, 95% CI 1.2 to 1.9; moderate/severe: RR 2.2, 95% CI 1.8 to 2.7) and RLD (RR 2.0, 95% CI 1.6 to 2.5) relative to normal lung function. These associations did not meaningfully change on applying follow-up lag times of 5, 10 and 15 years after spirometry. When analysed by histological type, associations with both COPD and RLD were stronger for squamous cell carcinoma and small cell carcinoma, and weaker for adenocarcinoma. Both COPD and RLD were associated with increased rates of total mortality.

Conclusions: Obstructive and restrictive impairments in lung function are associated with increased lung cancer risk.

Lung cancer is the leading cause of death from cancer in the world, with the highest incidence rates in Europe and North America.[1] Most lung cancers are attributable to tobacco smoking and, to a lesser extent, environmental tobacco smoke and occupational exposures; however, a small proportion of cases occur in non-smokers with no known environmental or occupational risk factors.[2] Other suspected risk factors for lung cancer include ionising radiation, air pollution, low consumption of fruits and vegetables, and genetic predisposition.[1]

Impaired lung function may also influence the development of lung cancer. Increased rates of this cancer have been consistently reported among individuals with non-malignant lung conditions such as chronic obstructive pulmonary disease (COPD), emphysema and asthma,[3–11] as well as milder deficits in lung function as measured by spirometry.[12–21] These associations persist even after adjustment for smoking, a major determinant of COPD and lung cancer. Although lung function seems to be predictive of subsequent lung cancer risk, there is debate over its pathogenetic significance. Some proposed mechanisms through which poor lung function may influence lung cancer risk include impaired pulmonary clearance of inhaled carcinogens[22] and inflammation-induced production of genotoxic reactive oxygen species (ROS).[23] It has also been suggested that these associations reflect the existence of inherited susceptibility factors common to both COPD and lung cancer.[24 25] However, there is still debate as to whether the observed relationships between impaired lung function and lung cancer are causal, or the product of residual confounding by smoking.

Most previous prospective investigations of impaired lung function and lung cancer risk have not attempted to investigate lung obstruction and restriction separately. Restrictive lung disease (RLD) is linked to a number of different conditions (eg, interstitial lung diseases, pleural disease, diabetes, obesity, cardiovascular disease, hypertension) and, unlike obstructive disease, is only weakly associated with smoking.[26] The only study to assess obstructive and restrictive disease separately, by Mannino *et al*,[5] found an increased risk for both types of impairment; however, the 50% excess lung cancer risk observed for restrictive disease did not reach statistical significance.

To elucidate further the relationship between lung function and lung cancer, we analysed data from a large cohort of Swedish construction workers who provided detailed data on smoking and underwent spirometric evaluation. Using the classification method of Mannino *et al*,[5] adapted from the Global Initiative for Chronic Obstructive Lung Disease criteria for COPD, we separately investigated obstructive lung diseases and RLDs as possible risk factors for lung cancer. We also investigated the relationship between lung function and specific histological types of lung cancer, and for three other outcomes: tobacco-related cancers arising at sites other than the lung, other cancers, and total mortality.

METHODS

Study population

This cohort has been described previously.[27 28] In 1968 the Swedish construction industry started the Organization for Working Environment, Occupational Safety and Health (in Sweden, *Bygghälsan*), a programme to offer nationwide health service to all employees of the Swedish construction

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 s; RLD, restrictive lung disease; ROS, reactive oxygen species

Table 1 Distributions of age at spirometry and smoking status in relation to lung function

	Lung function*					
		COPD				
	Normal, n (%)	Mild, n (%)	Moderate, n (%)	Severe, n (%)	Restrictive lung disease, n (%)	Total, n (%)
Age at spirometry (years)						
<20	19 559 (12)	98 (3)	177 (6)	7 (2)	1405 (18)	21 246 (12)
20–29	61 923 (38)	557 (16)	474 (16)	22 (6)	2079 (27)	65 055 (37)
30–39	37 744 (23)	714 (20)	378 (13)	34 (9)	1264 (16)	40 134 (23)
⩾40	43 240 (27)	2139 (61)	1926 (65)	323 (84)	2934 (38)	50 562 (29)
Smoking status						
Never smoked	82 462 (51)	964 (27)	725 (25)	65 (17)	3373 (44)	87 589 (49)
Former smoker	20 433 (13)	528 (15)	350 (12)	65 (17)	808 (11)	22 184 (13)
Current smoker	59 571 (37)	2016 (57)	1880 (64)	256 (66)	3501 (46)	67 224 (45)
Total	162 466 (92)	3508 (2)	2955 (2)	386 (<1)	7682 (4)	176 997 (100)

COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 s; n, number of cohort members; VC, vital capacity.
*Normal: $FEV_1/VC \geqslant 70\%$, $\%FEV_1 \geqslant 80\%$; mild COPD: $FEV_1/VC < 70\%$, $\%FEV_1 \geqslant 80\%$; moderate COPD: $FEV_1/VC < 70\%$, $\%FEV_1 = 50–79\%$; severe COPD: $FEV_1/VC < 70\%$, %FEV <50%; restrictive lung disease: $FEV_1/VC \geqslant 70\%$, $\%FEV_1 < 80\%$.

industry. As part of this programme, workers were invited to undergo regular health examinations; approximately 80% of eligible workers participated at least once. A computer registry includes examination data from 389 132 workers who were evaluated as part of *Bygghälsan* between 1971 and 1993.

Spirometry and other data collection

Starting in 1978, *Bygghälsan* health examinations usually included spirometric measurements of lung function.[29] Two measurements were recorded: forced expiratory volume in 1 s (FEV_1) and vital capacity (VC). The FEV_1 measure was also expressed as a percentage of the predicted FEV_1 ($\%FEV_1$) calculated from the adjusted European Community for Steel and Coal/European Respiratory Society prediction equations developed by Quanjer.[30] During this period, lung function was measured during 82–92% of all health examinations by trained staff using calibrated equipment. A minimum of three satisfactory measurements of FEV_1 and vital capacity were necessary, and these were required to be within 10% of each other. The highest of the three measurements was entered into a database. Following the method of Mannino *et al*,[5] we classified individuals into five categories of lung function according to FEV_1/VC and $\%FEV_1$: normal lung function ($FEV_1/VC \geqslant 70\%$, $\%FEV_1 \geqslant 80\%$), mild COPD ($FEV_1/VC < 70\%$, $\%FEV_1 \geqslant 80\%$), moderate COPD ($FEV_1/VC < 70\%$, $\%FEV_1$ 50–79%), severe COPD ($FEV_1/VC < 70\%$, %FEV <50%) and RLD ($FEV_1/VC \geqslant 70\%$, $\%FEV_1 < 80\%$).

Information on smoking history, body mass index and occupational exposures were also collected from cohort members. Data regarding smoking habits collected from the initial examination were used to ascertain smoking status (never, former, current smokers), smoking intensity, smoking duration and the number of pack-years smoked. When information on smoking habits was not available from the initial examination, information from a subsequent visit was used. Height and weight measurements from the earliest examination were used to calculate body mass index. Additionally, a job–exposure matrix was developed to assign exposures to selected agents (diesel exhaust, asbestos, organic solvents, metal dust, asphalt, wood dust, stone dust, mineral wool and cement dust) for >300 job codes in the industry[31] based on a survey of occupational exposures carried out by *Bygghälsan* from 1971 to 1976.

Statistical analysis

For our analysis, we linked the *Bygghälsan* computerised register of male participants (96% of all participants) to the Swedish National Cancer Registry through 2001 to identify first primary

Table 2 Relative risk of lung cancer by smoking status and lung function

Factor	Person-years	n	Adjusting for age RR (95% CI)	Multivariate adjustment* RR (95% CI)
Smoking				
Non-smoker	1 205 114	42	1.0	1.0
Former smoker	329 236	69	2.7 (1.9 to 4.0)	2.7 (1.8 to 3.9)
Current smoker (pack-years)	971 491	723	12.9 (9.4 to 16.6)	11.7 (8.5 to 15.9)
Current smoker, <50	495 987	115	9.1 (6.4 to 12.9)	8.5 (5.9 to 12.1)
Current smoker, ⩾50	134 322	243	20.6 (14.8 to 28.7)	18.0 (12.9 to 25.1)
Current smoker, unknown	341 182	365	11.9 (8.6 to 16.3)	10.9 (7.9 to 15.0)
Lung function†				
Normal	2 326 915	570	1.0	1.0
Mild COPD	50 384	70	2.1 (1.6 to 2.7)	1.5 (1.2 to 1.9)
Moderate COPD	38 585	90	3.3 (2.6 to 4.1)	2.1 (1.7 to 2.6)
Severe COPD	3 828	15	4.1 (2.4 to 6.8)	2.7 (1.6 to 4.6)
Restrictive lung disease	86 129	89	2.8 (2.3 to 3.5)	2.0 (1.6 to 2.5)

COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 s; VC, vital capacity.
*Rate ratios for smoking adjusted for age and lung function; rate ratios for lung function adjusted for age and smoking.
†Normal: $FEV_1/VC > 70\%$, $\%FEV_1 > 80\%$; mild COPD: $FEV_1/VC \leqslant 70\%$, $\%FEV_1 > 80\%$; moderate COPD: $FEV_1/VC \leqslant 70\%$, $\%FEV_1 = 51–80\%$; severe COPD: $FEV_1/VC \leqslant 70\%$, %FEV ⩽50%; restrictive disease: $FEV_1/VC > 70\%$, $\%FEV_1 \leqslant 80\%$.

cases of lung cancer (International Classification of Diseases, seventh revision codes 162, 163). To reduce the possible effect of undiagnosed lung cancer on spirometry readings, we began follow-up of subjects 2 years after the date of spirometry. Person-years for each cohort member were computed to the date of cancer diagnosis, death, emigration or 31 December 2001, whichever occurred first. We also excluded subjects missing information on spirometry readings and smoking status.

We used Poisson regression modelling using the software package EPICURE (v 1.4)[32] to calculate rate ratios (RR) and 95% confidence intervals (CI) relating lung cancer incidence to categories of lung function, adjusted for categories of age (<50, 50–59, 60–69 and ⩾70 years) and smoking (non-smoker; former smoker; current smoker, <20 pack-years; current smoker, ⩾20 pack-years; current smoker, pack-years unknown). Additional adjustment for body mass index (⩽18.5, 18.6–20.0, 20.1–22.5, 22.6–25.0, 25.1–27.5, 27.6–30.0, 30.1–35.0, >35.0 and missing) and occupational exposure to workplace agents had no material effect on the risk estimates for lung function; results adjusting for these variables are not presented. Analyses of lung function and lung cancer were repeated excluding the first 5, 10 and 15 years of follow-up to assess the sensitivity of our findings to the length of time since lung function measurement.

Additional analyses stratified by smoking status (non-smoker, former smoker, current smoker) were performed; analyses of former and current smokers were adjusted by smoking intensity and duration. We also investigated the relationship between lung function and rates of three other outcomes: non-lung smoking-related cancers (cancers of the lip, oral cavity, nasopharynx, pharynx, larynx, oesophagus, stomach, pancreas, kidney and urinary bladder), other cancers and overall mortality. Analyses of these end points were conducted, both overall adjusted for smoking and stratifying on smoking status. Analyses of overall mortality were additionally adjusted for body mass index.

The study was approved by the local committee of ethics at Umeå University and by the steering committee of the register.

RESULTS

Lung function measurements were available for 176 997 male workers; these workers contributed a total of 2 505 841 person-years of observation, yielding 834 incident cases of lung cancer. Table 1 shows the characteristics of the cohort, stratified by lung function category. Subjects with spirometric evidence of COPD were considerably older, on average, than individuals with normal lung function, and much more likely to smoke. The average age and prevalence of smoking among individuals with RLD were slightly higher than among those with normal lung function.

Table 2 summarises the relative risk of lung cancer in relation to smoking status and category of lung function. After adjusting for age, current smokers had a 13-fold greater risk of lung cancer than non-smokers, with a relative risk of 21 for those with ⩾50 pack-years. The age-adjusted relative risk of lung cancer increased monotonically with severity of COPD and was also significantly increased for evidence of RLD. On adjustment for smoking, the risk estimates for obstructive disease (RR 1.5, 2.1, 2.7 for mild, moderate and severe COPD, respectively) and restrictive disease (RR 2.0) were weaker, but remained increased and significant. The results did not meaningfully change when we excluded current smokers with unknown pack-years from the analysis (data not shown).

Table 3 presents the results of additional analyses of lung cancer and other outcomes by lung function category. The associations with obstructive and restrictive lung disease remained when we extended the lag time between spirometry measurement and start of follow-up to 5, 10 and 15 years. Analyses restricted to non-smokers were only marginally informative because of the sparse number of lung cancers diagnosed among individuals with impaired lung function, although RR estimates were generally increased for all categories of impaired lung function. A significantly increased risk of lung cancer was observed for mild COPD among former smokers. Among current smokers, both COPD and RLD were clearly associated with increased lung cancer risk.

We observed differences in the relationship with lung function by lung cancer histology. The strongest associations with COPD and RLD were observed for squamous cell carcinoma, small cell carcinoma and rare or unclassified lung cancers. By contrast, adenocarcinoma of the lung exhibited a weak, borderline statistically significant relationship with COPD, and was not associated with RLD. These differences by histology did not change when we restricted the analyses to current smokers (data not shown).

We also investigated the relationship with lung function for other outcomes (table 3). The relative risk of non-lung tobacco-related cancers was significantly increased for moderate or severe COPD, but not for RLD. No relationship between lung function and other cancers was observed. Excess risks of all-cause mortality were observed for both COPD and RLD.

DISCUSSION

In our prospective investigation of 176 997 male Swedish construction workers, we observed an increased risk of lung cancer among individuals with COPD and with RLD; these findings are consistent with those of previous studies investigating lung function and lung cancer.[3–5 12–21] Our observed relationships are unlikely to be the result of cancer-induced changes in lung function, as associations were apparent in time periods of follow-up >15 years after the date of spirometry.

The pathogenetic significance of the association between COPD and lung cancer has been the source of debate; in particular, it has been suggested that the relationship may be a product of residual confounding by smoking, the predominant risk factor for both COPD and lung cancer.[16] We controlled for the effects of smoking, conducting analyses adjusting for smoking intensity and duration. However, adjustment for these variables probably does not entirely capture the relationship between smoking and lung cancer. Analyses restricted to non-smokers are the most informative means of investigating whether COPD is independently associated with lung cancer. However, our relative risk estimates among non-smokers are very unstable, owing to the small number of lung cancers diagnosed in the COPD category (n = 3). Two other large cohort studies that investigated the relationship between impaired lung function and lung cancer among non-smokers, although also limited by small numbers, did not observe evidence of an association in this subgroup.[16 19]

Analyses stratified by lung cancer histology can also offer insight into the relationship between COPD and lung cancer, given the well-established finding that smoking is a stronger risk factor for squamous cell carcinoma and small cell carcinoma than for adenocarcinoma of the lung.[33] Our findings for COPD followed a similar pattern; associations were strongest for squamous cell carcinoma and small cell carcinoma and weakest for adenocarcinoma. Two other studies of lung function have reported similar histology-specific findings.[15 34] These differences by histology support the notion that tobacco smoke plays a part in the association between COPD and lung cancer. This is further substantiated by the observation that the non-lung tobacco-related cancers showed similar, albeit weaker, associations with COPD as for lung cancer, whereas no relationship with other cancers was observed.

Table 3 Relative risk of lung cancer, non-lung tobacco-related cancers, other cancers and all-cause mortality in relation to lung function

	Lung function*							
			COPD					
	Normal		Mild		Moderate/severe		Restrictive lung disease	
Outcome	n	RR	n	RR (95% CI)	n	RR (95% CI)	n	RR (95% CI)
Lung cancer								
Overall†	570	1.0	70	1.5 (1.2 to 1.9)	105	2.2 (1.8 to 2.7)	89	2.0 (1.6 to 2.5)
5-year lag time	518	1.0	61	1.5 (1.1 to 1.9)	88	2.1 (1.7 to 2.6)	85	2.2 (1.7 to 2.8)
10-year lag time	388	1.0	47	1.6 (1.1 to 2.1)	57	2.1 (1.6 to 2.7)	62	2.3 (1.8 to 3.1)
15-year lag time	211	1.0	26	1.7 (1.1 to 2.6)	27	2.3 (1.5 to 3.4)	31	2.6 (1.8 to 3.8)
Non-smokers‡	37	1.0	1	0.9 (0.1 to 6.7)	2	2.8 (0.7 to 11.9)	2	1.6 (0.4 to 6.8)
Former smokers§	56	1.0	7	2.2 (1.0 to 4.8)	1	0.3 (0.1 to 2.5)	5	1.7 (0.7 to 4.2)
Current smokers§	477	1.0	62	1.5 (1.1 to 1.9)	102	2.3 (1.9 to 2.9)	82	2.1 (1.7 to 2.7)
Adenocarcinoma†	162	1.0	16	1.3 (0.8 to 2.2)	20	1.6 (1.0 to 2.6)	9	0.8 (0.4 to 1.5)
SCC†	151	1.0	19	1.4 (0.9 to 2.3)	38	2.7 (1.9 to 3.8)	31	2.5 (1.7 to 3.7)
Small cell carcinoma†	77	1.0	13	2.2 (1.2 to 3.9)	10	1.6 (0.8 to 3.1)	17	2.9 (1.7 to 5.0)
Other/unclassified†	180	1.0	22	1.5 (0.9 to 2.3)	37	2.4 (1.7 to 3.5)	32	2.3 (1.6 to 3.4)
Non-lung tobacco-related cancers								
Overall†	1276	1.0	85	1.1 (0.9 to 1.3)	128	1.6 (1.4 to 2.0)	85	1.1 (0.9 to 1.4)
Non-smokers‡	265	1.0	10	1.3 (0.7 to 2.5)	7	1.4 (0.7 to 3.1)	6	0.7 (0.3 to 1.5)
Former smokers§	229	1.0	11	1.0 (0.6 to 1.9)	14	1.5 (0.9 to 2.6)	12	1.2 (0.6 to 2.1)
Current smokers§	782	1.0	64	1.0 (0.8 to 1.3)	107	1.7 (1.4 to 2.1)	67	1.1 (0.9 to 1.5)
Other cancers								
Overall†	4749	1.0	257	1.0 (0.9 to 1.1)	243	1.0 (0.9 to 1.1)	240	0.9 (0.8 to 1.1)
Non-smokers‡	1767	1.0	54	1.1 (0.8 to 1.4)	42	1.3 (1.0 to 1.8)	46	0.8 (0.6 to 1.0)
Former smokers§	966	1.0	48	1.0 (0.8 to 1.4)	44	1.1 (0.8 to 1.4)	49	1.1 (0.7 to 1.5)
Current smokers§	2016	1.0	155	0.9 (0.8 to 1.1)	157	0.9 (0.8 to 1.1)	145	1.0 (0.8 to 1.2)
All-cause mortality								
Overall¶	7659	1.0	561	1.2 (1.1 to 1.3)	845	1.9 (1.8 to 2.0)	668	1.4 (1.3 to 1.6)
Non-smokers**	1987	1.0	61	1.1 (0.8 to 1.4)	61	1.6 (1.2 to 2.1)	99	1.4 (1.1 to 1.7)
Former smokers††	1322	1.0	79	1.2 (0.9 to 1.5)	103	1.9 (1.6 to 2.4)	107	1.7 (1.4 to 2.1)
Current smokers††	4350	1.0	421	1.2 (1.1 to 1.4)	681	2.0 (1.8 to 2.1)	462	1.4 (1.3 to 1.6)

COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 s; SSC, squamous cell carcinoma; VC, vital capacity.
*Normal: $FEV_1/VC > 70\%$, $\%FEV_1 > 80\%$; mild COPD: $FEV_1/VC \leqslant 70\%$, $\%FEV_1 > 80\%$; moderate/severe COPD: $FEV_1/VC \leqslant 70\%$, $\%FEV_1 \leqslant 80\%$; restrictive lung disease: $FEV_1/VC > 70\%$, $\%FEV_1 \leqslant 80\%$.
†RR adjusted for attained age, smoking (non-smoker; former smoker; current smoker, <50 pack-years; current smoker, ⩾50 pack-years, current smoker, pack-years unknown).
‡RR adjusted for attained age.
§RR adjusted for attained age, smoking intensity and smoking duration.
¶RR adjusted for attained age, body mass index (⩽18.5, 18.6–20.0, 20.1–22.5, 22.6–25.0, 25.1–27.5, 27.6–30.0, 30.1–35.0, >35.0 and missing), smoking (non-smoker; former smoker; current smoker, <50 pack-years; current smoker, ⩾50 pack-years, current smoker, pack-years unknown).
**RR adjusted for attained age, body mass index.
††RR adjusted for attained age, body mass index, smoking intensity and smoking duration.

Several possible explanations for the observed relationship between COPD and lung cancer among smokers have been postulated. The possibility of residual confounding from smoking has been discussed previously. Another possible explanation is that impaired lung function may be an indicator of underlying conditions that increase the risk of smoking-induced lung cancer. One such condition may be inflammation of the airways, which can be caused by smoking; it possibly contributes to the pathogenesis of lung cancer[6 35–37] and is suspected to play a part in the decline in lung function observed among smokers and individuals with asthma and COPD.[38–41] It has also been proposed that decreased lung function may directly modify the relationship between smoking and lung cancer by reducing the effectiveness of lung clearance mechanisms.[22] It is well documented that mucociliary clearance, an important mechanism for removing inhaled particulates and respiratory tract secretions from the airways, is reduced in patients with obstructive respiratory diseases.[42] If mucociliary clearance is impaired, tobacco smoke particulates would be retained in the lungs for a longer period of time, effectively increasing the exposure of lung epithelium to tobacco smoke carcinogens.

We also observed excess rates of lung cancer among individuals with evidence of lung restriction from spirometry. To our knowledge, only one other study has also investigated lung restriction as a risk factor for lung cancer.[5] In that study, an increased relative risk for lung cancer was also observed, although not at a level of statistical significance. RLD, involving a decrease in total lung volume, is most notably caused by diseases of the lung parenchyma (eg, interstitial lung disease, pneumonitis) or of the chest wall or pleura. Evidence of restriction from spirometric evaluation of population samples has also been associated with a variety of chronic medical conditions, including diabetes, congestive heart failure, stroke, obesity and hypertension.[26] It is plausible that underlying inflammatory processes causing lung restriction could contribute to the pathogenesis of lung cancer.[6 35–37] Occupational exposure to asbestos and other workplace dusts may cause RLDs; however, our relative risk estimate was unaffected after controlling for a variety of occupational exposures, suggesting that confounding from these exposures does not explain our finding. It would also seem unlikely that our finding is a consequence of confounding from tobacco use, given the weak relationship between smoking and lung restriction observed in

this study and another general-population cohort.[26] Moreover, RLD was not associated with non-lung tobacco-related cancers, as might be expected if confounding by smoking was at play. However, the observed pattern of associations by histological subtype (association present for squamous cell carcinoma and small cell carcinoma, absent for adenocarcinoma) was compatible with that expected if residual confounding from smoking was present; consequently, we cannot definitively rule out such confounding as an explanation for our association between RLD and lung cancer.

We also observed increased rates of all-cause mortality among individuals with obstructive lung disease and RLD. The association was also present in non-smokers, suggesting that the associations are independent of tobacco smoke. An association between impaired lung function and mortality, and cardiovascular mortality in particular, has been previously reported in many studies.[17 19 43–51] Of the studies that performed informative analyses among non-smokers, most,[19 44–46 48] although not all,[50] observed an association with lung function in this subpopulation. The only other study to have differentiated between obstructive lung disease and RLD also found increased mortality in each group.[50] One possible explanation for a relationship between lung function and mortality is that impaired lung function is an indicator for underlying conditions or exposures associated with increased mortality. A causal relationship between COPD and cardiovascular mortality has also been proposed, whereby airway inflammation associated with obstructive respiratory disease induces a chronic systemic inflammatory response that contributes to the progression of atherosclerosis and cardiovascular disease.[51] Additionally, the increased risk of diabetes and metabolic syndrome among patients with COPD probably contributes to the increased cardiovascular mortality.[52 53]

The *Bygghälsan* cohort, with its large size, long period of follow-up and collection of detailed information on spirometry and smoking history, is exceptionally well suited to investigate the relationship between lung function and lung cancer. To our knowledge, this is the largest study to separately investigate obstructive and restrictive respiratory impairment in relation to subsequent risk of lung cancer and mortality. Additionally, the long period of follow-up enabled us to explore the sensitivity of our findings to different lag times between spirometry and follow-up, ruling out reverse causality as an explanation for our findings. However, a limitation of our study was the small number of lung cancer cases accrued among non-smokers with impaired lung function, which precluded meaningful investigation of lung cancer risk within this subgroup.

In conclusion, this large prospective study corroborates earlier findings suggesting that both obstructive and restrictive impairments in lung function are associated with increased lung cancer risk. The association with RLD, a condition only weakly linked to tobacco use, provides additional support for the hypothesis that inflammation in the lung may be an independent risk factor for lung cancer.

Authors' affiliations

Mark P Purdue, Michael C R Alavanja, Mary H Ward, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland, USA
Laura Gold, University of Washington School of Public Health and Community Medicine, Seattle, Washington, USA
Bengt Järvholm, Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden
Roel Vermeulen, Institute for Risk Assessment Sciences, Environmental Epidemiology, Utrecht University, Utrecht, The Netherlands

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LUNG ALERT

Inhaled corticosteroids and adrenal suppression in children

▲ Paton J, Jardine E, McNeill E, *et al*. Adrenal responses to low dose synthetic ACTH (Synacthen) in children receiving high dose inhaled fluticasone. *Arch Dis Child* 2006;**91**:808–13.

Inhaled corticosteroids (ICS) have been shown to cause clinical adrenal insufficiency. Following two serious cases of acute adrenal insufficiency due to ICS, Paton *et al* evaluated adrenal function in children prescribed fluticasone proprionate above the maximum UK licensed dose (>400 μg/day).

One hundred and ninety four children with asthma who were taking >500 μg/day fluticasone proprionate were tested using a low dose synacthen test (LDST). Responses to LDST were defined as normal (peak cortisol >500 $nmoll^{-1}$), impaired (peak <500 $nmoll^{-1}$) or flat (peak <500 $nmoll^{-1}$ with increment <200 $nmoll^{-1}$ and basal morning cortisol <200 $nmoll^{-1}$).

Six patients (3%) had a flat response, in 82 (42%) it was impaired and 104 (54%) had a normal response. All six patients who had a flat response were taking >1000 μg/day fluticasone proprionate. There was a weak but significant inverse correlation between peak cortisol and total daily dose ($r = -0.213$; $p = 0.002$). There was no relation between the number of rescue oral steroid courses and peak cortisol.

This study demonstrates that a significant proportion of children receiving fluticasone proprionate at above the licensed dose have biochemical adrenal suppression. Compliance with medications was not evaluated and therefore the effects of ICS on adrenal function may well have been underestimated.

J Steer
Specialist Registrar in Respiratory Medicine, Hartlepool, UK; john_steer@hotmail.com