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

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ABSTRACT

Background: While impaired lung function in general has been associated with an elevated risk of lung cancer, past studies typically have not attempted to separately investigate the obstructive and restrictive components of respiratory impairment. To further address this question, we analyzed data from a large (N=176,997) cohort of male Swedish construction workers for whom spirometry measurements prior to follow-up were available. Methods: Cancer incidence for 1971-2001 was obtained through linkage with the national cancer registry. Using a modification of the GOLD 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. We also investigated other endpoints (histologic types of lung cancer, non-lung tobacco-related cancers, other cancers, total mortality).

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 1.2-1.9; moderate / severe: RR 2.2, 95% CI 1.8-2.7) and RLD (RR 2.0, 95% CI 1.6-2.5) relative to normal lung function. These associations did not meaningfully change upon applying follow-up lag times of 5, 10 and 15 years after spirometry. When analyzed by histologic 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 elevated rates of total mortality. Conclusions: Obstructive and restrictive impairments in lung function are associated with increased lung cancer risk.
INTRODUCTION

Lung cancer is the leading cause of cancer death in the world, with the highest incidence rates in Europe and North America. [1] The majority of lung cancers is 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 ionizing radiation, air pollution, low consumption of fruits and vegetables and genetic predisposition. [1]

Impaired lung function may also influence the development of lung cancer. Elevated rates of this cancer have been consistently reported among individuals with nonmalignant 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. While lung function appears 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 the impaired pulmonary clearance of inhaled carcinogens [22] and the 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 separately investigate lung obstruction and restriction. Restrictive lung disease is linked to a number of different conditions (e.g., 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 separately assess obstructive and restrictive disease, 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 further elucidate the relationship between lung function and lung cancer, we analyzed data from a large cohort of Swedish construction workers who provided detailed smoking data and underwent spirometric evaluation. Using the classification method of Mannino et al., [5] adapted from the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria for COPD, we separately investigated obstructive and restrictive lung diseases as possible risk factors for lung cancer. We also investigated the relationship between lung function and specific histologic 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 previously described. [27, 28] Briefly, in 1968 the Swedish construction industry started the Organization for Working Environment, Occupational Safety and Health (in Sweden, Bygghälsan), a program to offer nationwide health service to all employees of the Swedish construction industry. As part of this program, workers were invited to undergo regular health examinations; approximately 80 percent 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 second (FEV₁) and vital capacity (VC). The FEV₁ measure was also expressed as a percentage of the predicted FEV₁ (%FEV₁) 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 FEV₁ and VC 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 FEV₁/VC and %FEV₁: normal lung function (FEV₁/VC ≥ 70%, %FEV₁ ≥ 80%), mild COPD (FEV₁/VC < 70%, %FEV₁ ≥ 80%), moderate COPD (FEV₁/VC < 70%, %FEV₁ 50% – 79%), severe COPD (FEV₁/VC < 70%, %FEV < 50%) and restrictive lung disease (FEV₁/VC ≥ 70%, %FEV₁ < 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 over 300 job codes in the industry [31] based on a survey of occupational exposures carried out by Bygghälsan from 1971 through 1976.

**Statistical Analysis**

For our analysis, we linked the Bygghälsan computerized register of male participants (96% of all participants) to the Swedish National Cancer Registry through 2001 to identify first primary 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 two years after the date of spirometry. Person-years for each cohort member were computed to the date of cancer diagnosis, death, emigration or December 31, 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 [32] to calculate rate ratios (RR) and 95 percent confidence intervals (CI) relating lung cancer incidence to categories of lung function, adjusted for categories of age (<50; 50-59; 60-69; 70+) 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, 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 endpoints were conducted both overall adjusted for smoking and stratifying upon 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. The characteristics of the cohort, stratified by lung function category, are shown in Table 1. 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 restrictive lung disease were slightly higher than among those with normal lung function.

The relative risk of lung cancer in relation to smoking status and category of lung function is summarized in Table 2. After adjusting for age, current smokers had a thirteen-fold greater risk of lung cancer than non-smokers, with a relative risk of 21 for those with 50 or more pack-years. The age-adjusted relative risk of lung cancer increased monotonically with severity of COPD and was also significantly elevated for evidence of restrictive lung disease. Upon 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 elevated and statistically significant. The results did not meaningfully change when we excluded current smokers with unknown pack-years from the analysis (data not shown).
Table 1: Distributions of age at spirometry and smoking status in relation to lung function

<table>
<thead>
<tr>
<th>COPD</th>
<th>Normal N (%)</th>
<th>Mild N (%)</th>
<th>Moderate N (%)</th>
<th>Severe N (%)</th>
<th>Total N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at Spirometry</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>19,559 (12)</td>
<td>98 (3)</td>
<td>177 (6)</td>
<td>7 (2)</td>
<td>1,405 (18)</td>
</tr>
<tr>
<td>20-29</td>
<td>61,923 (38)</td>
<td>557 (16)</td>
<td>474 (16)</td>
<td>22 (6)</td>
<td>2,079 (27)</td>
</tr>
<tr>
<td>30-39</td>
<td>37,744 (23)</td>
<td>714 (20)</td>
<td>378 (13)</td>
<td>34 (9)</td>
<td>1,264 (16)</td>
</tr>
<tr>
<td>40+</td>
<td>43,240 (27)</td>
<td>2,139 (61)</td>
<td>1,926 (65)</td>
<td>323 (84)</td>
<td>2,934 (38)</td>
</tr>
<tr>
<td>Smoking Status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoked</td>
<td>82,462 (51)</td>
<td>964 (27)</td>
<td>725 (25)</td>
<td>65 (17)</td>
<td>3,373 (44)</td>
</tr>
<tr>
<td>Former smoker</td>
<td>20,433 (13)</td>
<td>528 (15)</td>
<td>350 (12)</td>
<td>65 (17)</td>
<td>808 (11)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>59,571 (37)</td>
<td>2,016 (57)</td>
<td>1,880 (64)</td>
<td>256 (66)</td>
<td>3,501 (46)</td>
</tr>
<tr>
<td>Total</td>
<td>162,466 (92)</td>
<td>3,508 (2)</td>
<td>2,955 (2)</td>
<td>386 (&lt;1)</td>
<td>7,682 (4)</td>
</tr>
</tbody>
</table>

Abbreviations: N, number of cohort members; COPD, chronic obstructive pulmonary disease.

1 Normal: FEV1/VC ≥ 70%, %FEV1 ≥ 80%; Mild COPD: FEV1/VC < 70%, %FEV1 ≥ 80%; Moderate COPD: FEV1/VC < 70%, %FEV1 = 50% – 79%; Severe COPD: FEV1/VC < 70%, %FEV < 50%; Restrictive Lung Disease: FEV1/VC ≥ 70%, %FEV1 < 80%. 
Table 2: Relative risk of lung cancer by smoking status and lung function.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Person-Years</th>
<th>N</th>
<th>Adjusting for age: RR (95% CI)</th>
<th>Multivariate adjustment¹: RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Smoking</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-smoker</td>
<td>1,205,114</td>
<td>42</td>
<td>1.0 (1.0)</td>
<td>1.0</td>
</tr>
<tr>
<td>Former smoker</td>
<td>329,236</td>
<td>69</td>
<td>2.7 (1.9-4.0)</td>
<td>2.7 (1.8-3.9)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>971,491</td>
<td>723</td>
<td>12.9 (9.4-16.6)</td>
<td>11.7 (8.5-15.9)</td>
</tr>
<tr>
<td>Current smoker, &lt;50 pack-years</td>
<td>495,987</td>
<td>115</td>
<td>9.1 (6.4-12.9)</td>
<td>8.5 (5.9-12.1)</td>
</tr>
<tr>
<td>Current smoker, 50+ pack-years</td>
<td>134,322</td>
<td>243</td>
<td>20.6 (14.8-28.7)</td>
<td>18.0 (12.9-25.1)</td>
</tr>
<tr>
<td>Current smoker, pack-years unknown</td>
<td>341,182</td>
<td>365</td>
<td>11.9 (8.6-16.3)</td>
<td>10.9 (7.9-15.0)</td>
</tr>
<tr>
<td><strong>Lung Function</strong> ²</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>2,326,915</td>
<td>570</td>
<td>1.0 (1.0)</td>
<td>1.0</td>
</tr>
<tr>
<td>Mild COPD</td>
<td>50,384</td>
<td>70</td>
<td>2.1 (1.6-2.7)</td>
<td>1.5 (1.2-1.9)</td>
</tr>
<tr>
<td>Moderate COPD</td>
<td>38,585</td>
<td>90</td>
<td>3.3 (2.6-4.1)</td>
<td>2.1 (1.7-2.6)</td>
</tr>
<tr>
<td>Severe COPD</td>
<td>3,828</td>
<td>15</td>
<td>4.1 (2.4-6.8)</td>
<td>2.7 (1.6-4.6)</td>
</tr>
<tr>
<td>Restrictive Lung Disease</td>
<td>86,129</td>
<td>89</td>
<td>2.8 (2.3-3.5)</td>
<td>2.0 (1.6-2.5)</td>
</tr>
</tbody>
</table>

¹ Rate ratios for smoking adjusted for age and lung function; rate ratios for lung function adjusted for age and smoking.
² Normal: FEV1/VC > 70%, %FEV1 > 80%; Mild COPD: FEV1/VC ≤ 70%, %FEV1 > 80%; Moderate COPD: FEV1/VC ≤ 70%, %FEV1 = 51% – 80%; Severe COPD: FEV1/VC ≤ 70%, %FEV ≤ 50%; Restrictive Disease: FEV1/VC > 70%, %FEV1 ≤ 80%.

The results of additional analyses of lung cancer and other outcomes by lung function category are presented in Table 3. 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 due to the sparse number of lung cancers diagnosed among individuals with impaired lung function, although RR estimates were generally elevated 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 restrictive lung disease 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 restrictive lung diseases were observed for squamous cell carcinoma, small cell carcinoma and rare / unclassified lung cancers. In contrast, adenocarcinoma of the lung exhibited a weak, borderline statistically significant relationship with COPD, and was not associated with restrictive lung disease. 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 elevated for moderate / severe COPD but not for restrictive lung disease. No relationship between lung function and other cancers was observed. Excess risks of all-cause mortality were observed for both COPD and restrictive lung disease.
Table 3: Relative risk of lung cancer, non-lung tobacco-related cancers, other cancers, and all-cause mortality by % predicted FEV1 category.

<table>
<thead>
<tr>
<th>Lung Function</th>
<th>Normal</th>
<th>Mild</th>
<th>Moderate / Severe</th>
<th>Restrictive Lung Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung Cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall ^2</td>
<td>570</td>
<td>1.0</td>
<td>70 (1.5 1.2-1.9)</td>
<td>105 (2.2 1.8-2.7)</td>
</tr>
<tr>
<td>5-yr lag time</td>
<td>518</td>
<td>1.0</td>
<td>61 (1.5 1.1-1.9)</td>
<td>88 (2.1 1.7-2.6)</td>
</tr>
<tr>
<td>10-yr lag time</td>
<td>388</td>
<td>1.0</td>
<td>47 (1.6 1.1-2.1)</td>
<td>57 (2.1 1.6-2.7)</td>
</tr>
<tr>
<td>15-yr lag time</td>
<td>211</td>
<td>1.0</td>
<td>26 (1.7 1.1-2.6)</td>
<td>27 (2.3 1.5-3.4)</td>
</tr>
<tr>
<td>Non-smokers ^3</td>
<td>37</td>
<td>1.0</td>
<td>1 (0.9 0.1-6.7)</td>
<td>2 (2.8 0.7-11.9)</td>
</tr>
<tr>
<td>Former smokers ^4</td>
<td>56</td>
<td>1.0</td>
<td>7 (2.2 1.0-4.8)</td>
<td>1 (0.3 0.1-2.5)</td>
</tr>
<tr>
<td>Current smokers ^4</td>
<td>477</td>
<td>1.0</td>
<td>62 (1.5 1.1-1.9)</td>
<td>102 (2.3 1.9-2.9)</td>
</tr>
<tr>
<td>Adenocarcinoma ^2</td>
<td>162</td>
<td>1.0</td>
<td>16 (1.3 0.8-2.2)</td>
<td>20 (1.6 1.0-2.6)</td>
</tr>
<tr>
<td>SCC ^2</td>
<td>151</td>
<td>1.0</td>
<td>19 (1.4 0.9-2.3)</td>
<td>38 (2.7 1.9-3.8)</td>
</tr>
<tr>
<td>Small cell carcinoma ^2</td>
<td>77</td>
<td>1.0</td>
<td>13 (2.2 1.2-3.9)</td>
<td>10 (1.6 0.8-3.1)</td>
</tr>
<tr>
<td>Other / Unclassified ^2</td>
<td>180</td>
<td>1.0</td>
<td>22 (1.5 0.9-2.3)</td>
<td>37 (2.4 1.7-3.5)</td>
</tr>
<tr>
<td>Non-Lung Tobacco-Related Cancers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall ^2</td>
<td>1276</td>
<td>1.0</td>
<td>85 (1.1 0.9-1.3)</td>
<td>128 (1.6 1.4-2.0)</td>
</tr>
<tr>
<td>Non-smokers ^3</td>
<td>265</td>
<td>1.0</td>
<td>10 (1.3 0.7-2.5)</td>
<td>7 (1.4 0.7-3.1)</td>
</tr>
<tr>
<td>Former smokers ^4</td>
<td>229</td>
<td>1.0</td>
<td>11 (1.0 0.6-1.9)</td>
<td>14 (1.5 0.9-2.6)</td>
</tr>
<tr>
<td>Current smokers ^4</td>
<td>782</td>
<td>1.0</td>
<td>64 (1.0 0.8-1.3)</td>
<td>107 (1.7 1.4-2.1)</td>
</tr>
<tr>
<td>Other Cancers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall ^2</td>
<td>4749</td>
<td>1.0</td>
<td>257 (1.0 0.9-1.1)</td>
<td>243 (1.0 0.9-1.1)</td>
</tr>
<tr>
<td>Non-smokers ^3</td>
<td>1767</td>
<td>1.0</td>
<td>54 (1.1 0.8-1.4)</td>
<td>42 (1.3 1.0-1.8)</td>
</tr>
<tr>
<td>Former smokers ^4</td>
<td>966</td>
<td>1.0</td>
<td>48 (1.0 0.8-1.4)</td>
<td>44 (1.1 0.8-1.4)</td>
</tr>
<tr>
<td>Current smokers ^4</td>
<td>2016</td>
<td>1.0</td>
<td>155 (0.9 0.8-1.1)</td>
<td>157 (0.9 0.8-1.1)</td>
</tr>
<tr>
<td>All-Cause Mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall ^5</td>
<td>7659</td>
<td>1.0</td>
<td>561 (1.2 1.1-1.3)</td>
<td>845 (1.9 1.8-2.0)</td>
</tr>
<tr>
<td>Non-smokers ^6</td>
<td>1987</td>
<td>1.0</td>
<td>61 (1.1 0.8-1.4)</td>
<td>61 (1.6 1.2-2.1)</td>
</tr>
<tr>
<td>Former smokers ^7</td>
<td>1322</td>
<td>1.0</td>
<td>79 (1.2 0.9-1.5)</td>
<td>103 (1.9 1.6-2.4)</td>
</tr>
<tr>
<td>Current smokers ^7</td>
<td>4350</td>
<td>1.0</td>
<td>421 (1.2 1.1-1.4)</td>
<td>681 (2.0 1.8-2.1)</td>
</tr>
</tbody>
</table>

^1 Normal: FEV1/VC > 70%, %FEV1 > 80%; Mild COPD: FEV1/VC ≤ 70%, %FEV1 > 80%; Moderate / Severe COPD: FEV1/VC ≤ 70%, %FEV1 ≤ 80%; Restrictive Lung Disease: FEV1/VC > 70%, %FEV1 ≤ 80%.

^2 Rate ratios adjusted for attained age, smoking (non-smoker; former smoker; current smoker, <50 pack-years; current smoker, 50+ pack-years, current smoker, pack-years unknown).

^3 Rate ratios adjusted for attained age.

^4 Rate ratios adjusted for attained age, smoking intensity, smoking duration.

^5 Rate ratios 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, missing), smoking (non-smoker; former smoker; current smoker, <50 pack-years; current smoker, 50+ pack-years, current smoker, pack-years unknown).

^6 Rate ratios adjusted for attained age, body mass index.

^7 Rate ratios adjusted for attained age, body mass index, smoking intensity, smoking duration.
DISCUSSION

In our prospective investigation of 176,997 male Swedish construction workers, we observed an increased risk of lung cancer risk among individuals with COPD and with restrictive lung disease; 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 greater than 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 likely 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, due to the small number of lung cancers diagnosed in the COPD category (N=3). Two other large cohort studies that have investigated the relationship between impaired lung function and lung cancer among non-smokers, though 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 role 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, while no relation with other cancers was present.

A variety of 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 previously discussed. 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, possibly contributes to lung cancer pathogenesis, [6, 35-37] and is suspected to play a role 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.

Interestingly, 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 elevated relative
risk for lung cancer was also observed, though not at a level of statistical significance. Restrictive lung disease, involving a decrease in total lung volume, is most notably caused by diseases of the lung parenchyma (e.g. 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 lung cancer pathogenesis. [6, 35-37] Occupational exposure to asbestos and other workplace dusts may cause restrictive lung diseases; 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, restrictive lung disease 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 histologic 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 restrictive lung disease and lung cancer.

We also observed increased rates of all-cause mortality among individuals with obstructive- and restrictive lung disease. Interestingly, 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] though not all, [50] observed an association with lung function in this sub-population. The only other study to have differentiated between obstructive and restrictive lung disease also found elevated mortality rates 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 COPD patients likely contributes to the increased cardiovascular mortality rate. [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 sub-group.
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 restrictive lung disease, 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.

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