Airflow limitation increases lung cancer risk in smokers: the Lifelines cohort study

Running title: Airflow limitation and lung cancer risk.

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Conflict of Interest

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Abstract

Background: The relationship between smoking, airflow limitation and lung cancer occurrence is unclear. This study aims to evaluate the relationship between airflow limitation and lung cancer, and the effect modification by smoking status.

Methods: We included participants with spirometry data from Lifelines, a population-based cohort study from the Northern Netherlands. Airflow limitation was defined as FEV1/FVC ratio < 0.7. The presence of pathology-confirmed primary lung cancer during a median follow-up of 9.5 years was collected. The Cox regression model was used and hazard ratios (HR) with 95% confidence interval (95%CI) were reported. Adjusted confounders included age, sex, educational level, smoking, passive smoking, asthma status and asbestos exposure. The effect modification by smoking status was investigated by estimating the relative excess risk due to interaction (RERI) and the ratio of HRs with 95%CI.

Results: Out of 98,630 participants, 14,200 (14.4%) had airflow limitation. In participants with and without airflow limitation, lung cancer incidence was 0.8% and 0.2%, respectively. The adjusted HR between airflow limitation and lung cancer risk was 1.7 (1.4-2.3). The association between airflow limitation and lung cancer differed by smoking status [former smokers: 2.1 (1.4 - 3.2), current smokers: 2.2 (1.5-3.2)] and never smokers [0.9 (0.4-2.1)]. The RERI and ratio of HRs was 2.1 (0.7-3.4) and 2.5 (1.0-6.5) for former smokers, and 4.6 (95%CI: 1.8-7.4) and 2.5 (95%CI: 1.0-6.3) for current smokers, respectively.

Conclusions Airflow limitation increases lung cancer risk and this association is modified by smoking status.

Impact Ever smokers with airflow limitation are an important target group for the prevention of lung cancer.

Key words: lung function, lung cancer, population-based cohort, competing risk analysis, smoking.

Introduction

Both COPD and lung cancer are diseases mainly caused by tobacco smoking[1]. In a number of studies, an independent association between COPD or airflow limitation (could be caused by emphysema or chronic bronchitis) and lung cancer has been described[2–5]. Several studies show that after adjusting for smoking, impaired lung function is still a risk factor for lung cancer in heavy smokers recruited for lung cancer screening[2,3] or in construction workers[4], whereas, conversely, some researchers consider this association dependent on smoking or confounded by the residual effect of smoking[6–8]. Thus airflow limitation could be a concomitant and independent factor for lung cancer[9].

A recent cohort study in Korean population (≥ 40 years old) indicated that COPD was an independent risk factor for lung cancer incidence even in never smokers[10]. In that study, the COPD status was clinically assessed with the use of COPD medications. However, clinically-diagnosed COPD is more likely to be moderate-to-severe COPD[11], as in other studies it was found that in about half of the population with airflow limitation, COPD will be underdiagnosed[11–13]. Therefore, the use of clinically-diagnosed COPD may miss those with mild-to-moderate airflow limitation without clinical complaints. As screening spirometry is not routinely performed in a population without symptoms and/or risk factors, the evidence on the association between airflow limitation and lung cancer incidence in a general population is limited. Therefore, the objective of this study was to evaluate the relationship between airflow limitation and lung cancer risk as well as lung cancer subtype-specific risk in a large population-based cohort. Moreover, it was investigated whether the relationship between airflow limitation and lung cancer was modified by smoking status.

Materials and Methods

Study design

A population-based cohort study was conducted using data from Lifelines, which is a large longitudinal cohort study in the Northern Netherlands[14]. Lifelines started in 2006 and collected massive data from a representative 10% sample of the inhabitants from the Northern Netherlands, with the aim to establish a source for research on the development of chronic diseases and on healthy ageing. Between 2006 and 2013, over 167,000 inhabitants from the three northern provinces (Friesland, Groningen, and Drenthe) of the Netherlands were recruited for the Lifelines study[15]. The study protocol was approved by the medical ethics review committee of the University Medical Center Groningen, and the inclusion route was described thoroughly in a previous paper[15]. The adult population recruited for Lifelines study is broadly representative for the adult population of the north of the Netherlands[16]. For the current study, the characteristic of interest was airflow limitation at the baseline assessment and the outcome was lung cancer diagnosis during follow-up.

Study population

Adult participants (≥18 years old) with spirometry data at baseline were included. The following participants were excluded, 1) participants with technically invalid spirometry data, 2) participants with prevalent or prior history of lung cancer, 3) participants with missing values in any of the included covariates (see **Figure 1**). For a purpose of comparison with other published results in lung cancer screening populations, the analysis was additionally applied to a subset identified by applying the USPSTF criteria[17]. These criteria were: age between 50 and 80 years old, and either current smoker with ≥ 20 pack-years or former smoker with ≥ 20 pack-years and quit ≤ 15 years.

Airflow limitation

Pre-bronchodilator spirometry was performed using the Wellch Allyn SpiroPerfect device (Wellch allyn Version 1.6.0.489, PC- based SpiroPerfect with CardioPerfect Workstation software) according to American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines[18]. The measurements of Forced Expiratory Volume in One Second (FEV_1) and Forced Vital Capacity (FVC) were collected for this study. The Global Lung Initiative (GLI) 2012 equations were used to determine reference FEV1 values based on age, sex, height, and ethnicity[19] and everyone was treated as Caucasian. The percent predicted FEV1 (FEV_1 % predicted) was calculated from dividing FEV1 by reference FEV1. According to the Global Initiative on Chronic Obstructive Lung Disease (GOLD) criteria[20], airflow limitation was defined as a FEV1/FVC ratio < 0.7. The severity of airflow limitation was defined as follows, GOLD I (mild): FEV1 % predicted >80%; GOLD II (moderate): FEV1 % predicted = 50–79%; GOLD III (severe): FEV1 % predicted = 30–49%; GOLD IV (very severe): FEV1 % predicted < 30%.

Lung cancer

The Lifelines database was linked with the nationwide network and registry of histo- and cytopathology in the Netherlands (PALGA-Foundation). PALGA covers all pathology departments and institutes in the Netherlands and provides high-quality and accurate pathology data[21]. The linked database included cancer diagnoses until 26 January 2021. After linkage, an expert pulmonary pathologist reviewed all diagnoses regarding lung cancer. The conclusion of primary lung cancer was concluded from the pathological results. Patients with a diagnosis of mesothelioma and metastatic cancers to the lung were not regarded as primary lung cancer cases.

Included covariates

Self-reported data on age, sex, educational level, smoking, passive smoking, asthma status at the time of spirometry, and asbestos exposure were included in the study[22]. Smoking status at baseline was classified as never smokers (never smoked or smoked for < 1 year); former smokers (smoked for ≥ 1 year and quit smoking for ≥ 1 month) and current smokers (current smoker or quit smoking < 1 month)[23,24]. For smokers, pack-years of smoking were calculated by multiplying the number of packs of cigarettes smoked per day by the number of years the person has smoked (1 pack = 20 cigarettes). Passive smoking was defined based on the question "Have you been regularly exposed to tobacco smoke from others in the past 12 months". The asbestos exposure was defined according to the International Job Exposure Matrix for Asbestos[25] based on the self-reported occupation.

Statistical analysis

The baseline characteristics were descriptively compared between the included and non-included participants at baseline, and were also stratified by the airflow limitation status for the included participants. The probability of lung cancer occurrence by airflow limitation status across age was visualized using the complement of the Kaplan-Meier curve. Cox proportional hazards regression model was used to investigate the association between airflow limitation and lung cancer (subtype-specific) risk, in which age was the time scale (model 1). Age was used as the time scale in this study because occurrence of airflow limitation and lung cancer is both strongly determined by age. To tightly control the effect of age, age (baseline age + years in study) as the time scale was recommended[26]. Furthermore, using time-on-study as time scale was not relevant because entry the cohort did not modify the risk of lung cancer. The years in study was defined as the years between lung function assessment at baseline (from 2006 to 2013) and lung cancer

occurrence or death or the linkage date (26 January 2021), whichever came first. The included covariates were adjusted with a stepwise approach. Model 2 adjusted for smoking status and pack-years in addition to model 1, and model 3 adjusted for the remaining covariates in addition to model 2. Separate Cox regression models for each histological type of lung cancer were also fitted. Due to small numbers these models were adjusted for sex, and smoking status and pack-years only. Hazard ratios (HRs) with 95% confidence interval (95% CI) were reported. The effect modification by smoking status of the relationship between airflow limitation and lung cancer risk was investigated by estimating the relative excess risk due to interaction (RERI) on an additive scale and the ratio of HRs on a multiplicative scale and their 95% CIs ($RERI=HR_{11}-HR_{10}-HR_{01}+1$; ratio of $HRs=HR_{11}/(HR_{10}*HR_{01})$)[27]. A RERI of zero indicates there is no additive interaction, and that a ratio of HRs equals one indicates there is no multiplicative interaction. All analyses were performed using R version 4.0.2.

Sensitivity analysis

The GLI of European Respiratory Society recommends to define airflow limitation as FEV1/FVC less than the lower limit of normal (LLN) for each individual[19]. The LLN represents the lower 5% of test results from a normal population and is a function of age, sex, height and ethnicity[19]. To explore the effect of a different definition of airflow limitation on the association between airflow limitation and lung cancer incidence, a sensitivity analysis was therefore performed. In addition, the relationship between airflow limitation and lung cancer was examined in a subset of participants aged ≥ 50 years.

Data Availability Statement

The data of this study are available from the Lifelines cohort study upon reasonable request. For access to the data that support the findings of this study, the Lifelines research office can be contacted via www.lifelines.nl/researcher.

Results

Characteristics of participants at baseline

The baseline characteristics of the included participants were similar to those not included in this study (**Table S1**). Among the included 98,630 participants, 21.1% (20,849) were current smokers (mean pack-years: 14.6 ± 11.4), and 32.8% (32,351) were former smokers (mean pack-years: 9.8 ± 9.9, quitting years of smoking: 15.7 ± 11.6). The prevalence of airflow limitation was 14.4% (14,200) in all included population, and was 20.7% (4326), 17.3% (5582) and 9.4% (4292) in current, former and never smokers, respectively. Of the participants with airflow limitation, 65.7%, 32.8% and 1.5% had mild, moderate and severe airflow limitation, respectively. Compared with participants with normal lung function, those with airflow limitation were older, more likely male, less educated, and more likely to be a smoker (**Table 1**).

Airflow limitation and lung cancer risk

Primary lung cancer was diagnosed in 271 (0.3%) participants during the median follow-up of 9.5 (IQR:8.7-10.7) years, majority were adenocarcinoma (52.8%) and squamous cell carcinoma (21.4%). The mean diagnosis age was 61.1 ± 10.2 years old (**Table S2**). In the participants with and without airflow limitation, lung cancer incidence was 0.8% (112/14,200) and 0.2% (159/84,430), respectively (**Table 2**). The probability of lung cancer occurrence in participants with and without airflow limitation across age was visualized in **Figure S1**. The characteristics of included participants and lung cancer cases by smoking status are presented in **Table S3**.

After adjusting for smoking and other included covariates, the HR between airflow limitation and lung cancer risk in the entire cohort was 1.7 (95% CI: 1.4-2.3). Increasing severity of airflow limitation was associated with increased risk of lung cancer, with the HR for mild, moderate and

185 severe airflow limitation at 1.5 (95% CI: 1.1-2.1), 2.1 (95% CI: 1.5-2.9) and 3.7 (95% CI: 1.6-
186 8.5), respectively ($P_{trend} < 0.001$) (**Table 2**). When analyzed by histological subtype of lung
187 cancer, airflow limitation was associated with an increased risk of both adenocarcinoma (1.8, 95%
188 CI: 1.2-2.5) and squamous cell carcinoma (2.3, 95% CI: 1.4-4.0) (**Table 3**).

189 In the subset of a lung cancer screening population, airflow limitation was associated with 2.0-
190 fold risk of lung cancer, with the adjusted HR of 2.0 (95% CI: 1.2-3.3) (**Table 4**).

191 ## Effect modification by smoking status of the association between airflow limitation and lung
192 ## cancer risk

193 The multivariable analysis showed that the HR for the association between airflow limitation and
194 lung cancer was 0.9 (95% CI: 0.4-2.1) in never smokers, 2.1 (95% CI: 1.4-3.2) in former smokers,
195 and 2.2 (95% CI: 1.5-3.2) in current smokers (**Table 5**). The RERI was 2.1 (95%CI: 0.7-3.4) for
196 former smokers and 4.6 (95%CI: 1.8-7.4) for current smokers, which means that there was
197 positive effect modification by smoking status of the association between airflow limitation and
198 lung cancer risk on an additive scale. On a multiplicative scale, the ratio of HRs was 2.5 (95%CI:
199 1.0-6.5) for former smokers and 2.5 (95%CI: 1.0-6.3) for current smokers, which means that the
200 estimated effect of airflow limitation on the hazard ratio scale in the presence of current/former
201 smoking was larger than the estimated effect of airflow limitation in the absence of smoking.

202 ## Sensitivity analysis

203 The GLI-defined airflow limitation was associated with an increased risk of lung cancer, with the
204 adjusted HR of 1.7 (95% CI: 1.3-2.3). The analysis in the subset of participants aged ≥ 50 years
205 showed the adjusted HR of 1.8 (95% CI: 1.3-2.4) (**Table S4**).

Discussion

In this analysis we found that airflow limitation was associated with an increased risk of lung cancer, and this relationship differed by smoking status. The relationship between airflow limitation and lung cancer was more pronounced in smokers, even if they stopped smoking, when compared to never smokers. In addition, airflow limitation was associated with an increased risk for both adenocarcinoma and squamous cell carcinoma.

The association between the presence of airflow limitation and increased risk of lung cancer was observed in the entire cohort (adjusted HR=1.7, 95% CI: 1.4-2.3), and in the subset of a lung cancer screening eligible population (HR=2.0, 95% CI: 1.2-3.3). This is in line with other cohort studies in lung cancer screening populations of heavy smokers[3,28]. In addition, we observed a dose-response relationship for airflow limitation severity and lung cancer risk($P_{trend} < 0.001$), although the number of lung cancer cases was small in the group of participants with severe airflow limitation (6 out of 219).

Although we did not observe a significant association between the presence of airflow limitation and lung cancer in never smokers, this should be explained with caution. In our study, a predominant proportion (70%) of never smokers with airflow limitation had mild airflow limitation and only six lung cancer cases occurred in never smokers with airflow limitation. Moreover, the causes of airflow limitation could be different in never smokers and smokers. In never smokers the smaller airways relative to lung size in early life could be the reason for airflow limitation in later life[29], and such airflow limitation may not be associated with increased lung cancer risk[30]. On the other hand, smoking induced airflow limitation is probably caused by small airway narrowing (chronic bronchitis) and destruction of lung parenchyma (emphysema), which are associated with increased lung cancer risk[31]. The potential different causes of airflow

limitation in never smokers and smokers could be an explanation for the effect modification by smoking status. Spirometry data for never smokers are rarely and inconsistently reported in the literature. A study using data from the UK Biobank aiming to predict lung cancer suggested that the FEV1 was strongly associated with 2-year lung cancer risk in both smokers and never smokers[32]. In contrast, another study also using UK Biobank data, in which lung cancer diagnosis within 2 years were excluded, reported that incorporating FEV1/FVC had limited and insignificant added value for predicting 3-, 5- and 7-year lung cancer incidence in never smokers[33]. A study in Korean never smokers suggested that clinically diagnosed COPD, which were likely moderate-to-severe airflow limitation, was associated with the incidence of lung cancer[10]. However for a proper analysis of such association, passive smoking and work-related exposure should have also been taken into account.

The exact mechanisms underlying the increased risk of lung cancer among patients with airflow limitation/COPD are yet to be clearly defined. With respect to the development of both COPD and lung cancer there are increasing indications supporting the role of aging lung, oxidative stress (resulting in DNA damage and inflammation), telomere shortening and genetic predisposition, and immune dysfunction[1,9]. The chronic inflammation induced by current and past smoke exposure, in addition to the carcinogenic effects of smoke, is suggested to be a main driver to the pathogenesis of lung cancer in the setting of COPD[9,34]. Airflow limitation, when combined with smoking, allows prolonged contact of cigarette smoke components to the airway wall and other areas of the lung, this way increasing risk of DNA damage and cancer development. In addition, the chronic inflammation might be worsened upon exposure to tobacco smoke[35] and remains in COPD even after stopping smoking. As a consequence, this sustained inflammation can increase the probability of lung tumourigenesis[36] by producing proliferation inducing mediators. This

might explain the effect modification by ever smoking of the relationship between airflow limitation and lung cancer.

The presence of airflow limitation increased the risk of both adenocarcinoma and squamous cell carcinoma, with similar HRs. Previous studies about the association between airflow limitation and histology-specific lung cancer are inconsistent[4,37–39]. On one hand, a clinical study in patients with resectable NSCLC showed that the presence of airflow limitation was associated with a 4-fold increased risk for having squamous cell carcinoma compared with adenocarcinoma after adjusting for smoking and pack-years (OR=4.05, 95% CI: 1.93-10.57)[37]. Another study showed that in a cohort of construction workers, that association was the strongest for squamous-cell carcinoma (RR=2.7, 95% CI: 1.9-3.8) and the weakest for adenocarcinoma (RR=1.6, 95% CI: 1.0-2.6)[4]. On the other hand, a recent study in post-menopausal women suggested that the association between self-reported COPD and lung cancer was similar across histological subtypes, with HR ranging from 1.31-2.16[39]. That might in part be due to the shifting trend from squamous cell carcinoma to adenocarcinoma as a result of the predominant use of filtered cigarettes. We did not see an increased risk of small cell lung carcinoma probably due to the small number of cases, although other studies reported that airflow limitation was also positively associated with the risk of small cell lung carcinoma[4,39]. Further studies are warranted to clarify the association between airflow limitation and lung cancer subtype.

There are several strengths of this study. **First**, we defined a large population-based cohort study in a general population from a European country. Given that most of the evidence on lung cancer risk associated with airflow limitation was shown in the US population and in heavy smokers for lung cancer screening, our study further extended the association to a population including non-heavy smokers. **Second**, lung function data collected from spirometry were reviewed and

checked for technical correctness by the trained staff and only valid spirometry data were included for analysis. **Third**, we linked the population in Lifelines database with the PALGA network, which has a 100% coverage of the pathology departments and institutions in the Netherlands. Therefore, the diagnosis of lung cancer in our study was pathology-confirmed for all patients and the histological types were available for the analysis.

There are also some limitations of the study. **First**, we have considered the important confounders in the analysis of the relationship between airflow limitation and lung cancer, and demonstrated in the sensitivity analysis that age was well adjusted, although the diagnosis age of lung cancer in the present study (61 years) was relatively lower than in general population (around 70 years). However, due to the inherent limitation of an observational cohort study, other potential confounding factors, which were not taken into account, may affect the results. **Second**, the number of lung cancer cases in never smokers was small, which might result in a low power for statistical significance detection. **Third**, every included individual was treated as Caucasian when calculating the reference FEV1 values[40]. Despite of that, the effect on the conclusion was very limited since only 1.5% of Lifelines participants were non-Western migrants[16]. **Fourth**, the use of a fixed cut-off value for defining airflow limitation may lead to the potential misclassification[41]. However, the sensitivity analysis with an individual-based cut-off for airflow limitation still demonstrated the association.

In conclusion, airflow limitation is associated with an increased risk of lung cancer, and such association is more pronounced in smokers, even if they stopped smoking, than in never smokers. In addition, airflow limitation is associated with an increased risk of squamous cell carcinoma as well as adenocarcinoma of lung. The findings in this study implicate that former and current smokers with airflow limitation are important target groups for the prevention of lung cancer.

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References

1. Parris BA, O'Farrell HE, Fong KM, Yang IA. Chronic obstructive pulmonary disease (COPD) and lung cancer: Common pathways for pathogenesis. *J Thorac Dis*. 2019;11(Suppl 17):S2155-S2172. doi:10.21037/jtd.2019.10.54

2. De Torres JP, Bastarrika G, Wisnivesky JP, Alcaide AB, Campo A, Seijo LM, et al. Assessing the relationship between lung cancer risk and emphysema detected on low-dose CT of the chest. *Chest*. 2007;132(6):1932-1938. doi:10.1378/chest.07-1490

3. Wilson DO, Weissfeld JL, Balkan A, Schragin JG, Fuhrman CR, Fisher SN, et al. Association of radiographic emphysema and airflow obstruction with lung cancer. *Am J Respir Crit Care Med*. 2008;178(7):738-744. doi:10.1164/rccm.200803-435OC

4. Purdue MP, Gold L, Järvholm B, Alavanja MC, Ward MH, Vermeulen R. Impaired lung function and lung cancer incidence in a cohort of Swedish construction workers. *Thorax*. 2007;62(1):51-56. doi:10.1136/thx.2006.064196

5. de Torres JP, Marín JM, Casanova C, Cote C, Carrizo S, Cordoba-Lanus E, et al. Lung Cancer in Patients with Chronic Obstructive Pulmonary Disease Incidence and Predicting Factors. *Am J Respir Crit Care Med*. 2011;184:913-919. doi:10.1164/rccm.201103-0430OC

6. Powell HA, Iyen-Omofoman B, Baldwin DR, Hubbard RB, Tata LJ. Chronic obstructive pulmonary disease and risk of lung cancer: The importance of smoking and timing of diagnosis. *J Thorac Oncol*. 2013;8(1):6-11. doi:10.1097/JTO.0b013e318274a7dc

7. Powell HA, Iyen-Omofoman B, Baldwin DR, Hubbard RB, Tata LJ. Chronic obstructive pulmonary disease and risk of lung cancer: The importance of smoking and timing of diagnosis. *J Thorac Oncol*. 2013;8(4):e34-5. doi:10.1097/JTO.0b013e31828950e3

8. Molins L, Agusti À. Chronic obstructive pulmonary disease and risk of lung cancer: The importance of smoking and timing of diagnosis. *J Thorac Oncol*. 2013;8(4):e34. doi:10.1097/JTO.0b013e318286c1c1

9. Durham AL, Adcock IM. The relationship between COPD and lung cancer. *Lung Cancer*. 2015;90(2):121-127. doi:10.1016/j.lungcan.2015.08.017

10. Park HY, Kang D, Shin SH, Yoo KH, Rhee CK, Suh GY, et al. Chronic obstructive pulmonary disease and lung cancer incidence in never smokers: a cohort study. *Thorax*. 2020;75(6):506-509. doi:10.1136/thoraxjnl-2019-213732

11. Young RP, Hopkins RJ, Gamble GD, Silvestri GA. Incorporating baseline lung function in lung cancer screening: Does a "lung health check" help predict outcomes? *Chest*. 2020. doi:10.1016/j.chest.2020.10.070

12. Balata H, Harvey J, Barber PV, Colligan D, Duerden R, Elton P, et al. Spirometry performed as part of the Manchester community-based lung cancer screening programme detects a high prevalence of airflow obstruction in individuals without a prior diagnosis of COPD. *Thorax*. 2020;75(8):655-660. doi:10.1136/thoraxjnl-2019-213584

13. Hill K, Goldstein RS, Guyatt GH, Blouin M, Tan WC, Davis LL, et al. Prevalence and underdiagnosis of chronic obstructive pulmonary disease among patients at risk in primary care. *CMAJ*. 2010;182(7):673-678. doi:10.1503/cmaj.091784

14. Lifelines Biobank. https://www.lifelines.nl/. Accessed December 28, 2020.

15. Scholtens S, Smidt N, Swertz MA, Bakker SJ, Dotinga A, Vonk JM, et al. Cohort Profile: LifeLines, a three-generation cohort study and biobank. *Int J Epidemiol*. 2015;44(4):1172-1180. doi:10.1093/ije/dyu229

16. Klijs B, Scholtens S, Mandemakers JJ, Snieder H, Stolk RP, Smidt N. Representativeness of the LifeLines Cohort Study. *PLoS One*. 2015;10(9). doi:10.1371/JOURNAL.PONE.0137203

17. Krist AH, Davidson KW, Mangione CM, Barry MJ, Cabana M, Caughey AB, et al. Screening for Lung Cancer: US Preventive Services Task Force Recommendation Statement. *JAMA*. 2021;325(10):962. doi:10.1001/jama.2021.1117

18. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. *Eur Respir J*. 2005;26(2):319-338. doi:10.1183/09031936.05.00034805

19. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: The global lung function 2012 equations. *Eur Respir J*. 2012;40(6):1324-1343. doi:10.1183/09031936.00080312

20. Vogelmeier CF, Criner GJ, Martinez FJ, Anzueto A, Barnes PJ, Bourbeau J, et al. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2017 Report. GOLD Executive Summary. *Am J Respir Crit Care Med*. 2017;195(5):557-582. doi:10.1164/rccm.201701-0218PP

21. Home | Palga.nl. https://www.palga.nl/en/. Accessed June 11, 2021.

22. Stolk RP, Rosmalen JGM, Postma DS, de Boer RA, Navis G, Slaets JP, et al. Universal risk factors for multifactorial diseases: LifeLines: A three-generation population-based study. *Eur J Epidemiol*. 2008;23(1):67-74. doi:10.1007/s10654-007-9204-4

23. Questionnaires and protocols | ECRHS. https://www.ecrhs.org/questionnaires-and-protocols. Accessed February 10, 2022.

24. Faruque MO, Vonk JM, Bultmann U, Boezen HM. Airborne occupational exposures and inflammatory biomarkers in the Lifelines cohort study. *Occup Env Med*. 2020. doi:10.1136/oemed-2020-106493

25. Uribe J, Takahashi K, Ramos-Bonilla JP, Valenzuela MM, Giraldo MM, Infante DS. *International Job Exposure Matrix for Asbestos-IJEMA*.

26. Thiébaut ACM, Bénichou J. Choice of time-scale in Cox's model analysis of epidemiologic cohort data: A simulation study. *Stat Med*. 2004;23(24):3803-3820. doi:10.1002/sim.2098

27. Knol MJ, VanderWeele TJ. Recommendations for presenting analyses of effect modification and interaction. *Int J Epidemiol*. 2012;41(2):514-520. doi:10.1093/ije/dyr218

28. Hopkins RJ, Duan F, Chiles C, Greco EM, Gamble GD, Aberle D, et al. Reduced expiratory flow rate among heavy smokers increases lung cancer risk: Results from the national lung screening trial-American college of radiology imaging network cohort. *Ann Am Thorac Soc*. 2017;14(3):392-402. doi:10.1513/AnnalsATS.201609-741OC

29. Smith BM, Kirby M, Hoffman EA, Kronmal RA, Aaron SD, Allen NB, et al. Association of Dysanapsis With Chronic Obstructive Pulmonary Disease Among Older Adults. *JAMA*. 2020;323(22):2268-2280. doi:10.1001/JAMA.2020.6918

30. Thomsen M, Nordestgaard BG, Vestbo J, Lange P. Characteristics and outcomes of chronic obstructive pulmonary disease in never smokers in Denmark: A prospective population study. *Lancet Respir Med*. 2013;1(7):543-550. doi:10.1016/S2213-2600(13)70137-1/ATTACHMENT/355EB1AA-C18F-4F64-9106-B885D8FFCFDB/MMC1.PDF

31. Denholm R, Schüz J, Straif K, Stücker I, Jöckel KH, Brenner DR, et al. Is previous respiratory disease a risk factor for lung cancer? *Am J Respir Crit Care Med*. 2014;190(5):549-559. doi:10.1164/RCCM.201402-0338OC/SUPPL_FILE/DISCLOSURES.PDF

32. Muller DC, Johansson M, Brennan P. Lung Cancer Risk Prediction Model Incorporating Lung Function: Development and Validation in the UK Biobank Prospective Cohort Study. *J Clin Oncol*. 2017;35(8):861-869. doi:10.1200/jco.2016.69.2467

33. Warkentin MT, Lam S, Hung RJ. Determinants of impaired lung function and lung cancer prediction among never-smokers in the UK Biobank cohort. *EBioMedicine*. 2019;47:58-64. doi:10.1016/j.ebiom.2019.08.058

34. Molecular genetic studies in epithelial cells of lung cancer and COPD patients — the University of Groningen research portal. https://research.rug.nl/en/publications/molecular-genetic-studies-in-epithelial-cells-of-lung-cancer-and-. Accessed June 25, 2021.

35. Mark NM, Kargl J, Busch SE, Yang GH, Metz HE, Zhang H, et al. Chronic obstructive pulmonary disease alters immune cell composition and immune checkpoint inhibitor efficacy in non-small cell lung cancer. *Am J Respir Crit Care Med*. 2018;197(3):325-336. doi:10.1164/rccm.201704-0795OC

36. Chang SH, Mirabolfathinejad SG, Katta H, Cumpian AM, Gong L, Caetano MS, et al. T helper 17 cells play a critical pathogenic role in lung cancer. *Proc Natl Acad Sci U S A*. 2014;111(15):5664-5669. doi:10.1073/pnas.1319051111

37. Papi A, Casoni G, Caramori G, Guzzinati I, Boschetto P, Ravenna F, et al. COPD increases the risk of

squamous histological subtype in smokers who develop non-small cell lung carcinoma. *Thorax*. 2004;59(8):679-681. doi:10.1136/thx.2003.018291

38. Young R, Hopkins R. Lung function predicts lung cancer. *Eur Respir J*. 2010;35(6):1421-1422. doi:10.1183/09031936.00009410

39. Nagasaka M, Lehman A, Chlebowski R, Haynes BM, Ho G, Patel M, et al. COPD and lung cancer incidence in the Women's Health Initiative Observational Study: A brief report. *Lung Cancer*. 2020;141:78-81. doi:10.1016/j.lungcan.2020.01.006

40. spirometry_validation [Lifelines Wiki]. http://wiki-lifelines.web.rug.nl/doku.php?id=spirometry_validation&s[]=spirometry. Accessed May 24, 2021.

41. Swanney MP, Ruppel G, Enright PL, Pedersen OF, Crapo RO, Miller MR, et al. Using the lower limit of normal for the FEV1/FVC ratio reduces the misclassification of airway obstruction. *Thorax*. 2008;63(12):1046-1051. doi:10.1136/thx.2008.098483

Table 1 Baseline characteristics of study participants by airflow limitation status

Baseline characteristics	Airflow limitation (n=14,200)		Normal lung function (n=84,430)	
	Overall, n (%)	Lung cancer cases, n (%)	Overall, n (%)	Lung cancer cases, n (%)
Sex				
Men	6,970 (49.1)	63 (56.3)	33,585 (39.8)	64 (40.3)
Women	7,230 (50.9)	49 (43.7)	50,845 (60.2)	95 (59.7)
Age (mean ± SD)	51.0 ± 11.9	58.2 ± 9.9	42.9 ± 11.9	53.0 ± 10.1
< 50 years	6,961 (49.0)	27 (24.1)	62,697 (74.2)	68 (42.8)
≥ 50 years	6,915 (48.7)	82 (73.2)	21,346 (25.3)	89 (56.0)
≥ 75 years	324 (2.3)	3 (2.7)	387 (0.5)	2 (1.3)
Education[#]				
Low education	3,107 (21.9)	40 (35.7)	11,973 (14.2)	43 (27.0)
Medium education	7,346 (51.7)	53 (47.3)	45,457 (53.8)	75 (47.2)
High education	3,585 (25.2)	18 (16.1)	26,209 (31.0)	39 (24.5)
Unclassifiable	162 (1.1)	1 (0.9)	791 (1.0)	2 (1.3)
Smoking status				
NS	4,292 (30.2)	6 (5.4)	41,138 (48.7)	37 (23.3)
FS with ≤ 10 quit years	2,108 (14.8)	27 (24.1)	10,934 (13.0)	22 (13.8)
FS with 10-20 quit years	1,333 (9.4)	8 (7.1)	7,210 (8.5)	11 (6.9)
FS with > 20 quit years	2,114 (14.9)	11 (9.8)	8,515 (10.1)	31 (19.5)
FS with unknown quit years	27 (0.2)	0 (0.0)	110 (0.1)	0 (0.0)
FS with ≤ 10 PY	2,646 (18.6)	8 (7.1)	17,565 (20.8)	28 (17.6)
FS with 10-20 PY	1,391 (9.8)	5 (4.5)	5,765 (6.8)	20 (12.6)
FS with > 20 PY	1,325 (9.3)	31 (27.7)	2,586 (3.1)	15 (9.4)
FS with unknown PY	247 (1.5)	2 (1.8)	853 (1.0)	1 (0.6)
CS with ≤ 10 PY	776 (5.5)	2 (2.3)	7,306 (8.7)	10 (6.3)
CS with 10-20 PY	1,364 (9.7)	15 (13.4)	4,936 (5.8)	11 (6.9)
CS with > 20 PY	1,845 (13.0)	36 (32.1)	3,113 (3.7)	31 (19.5)
CS with unknown PY	341 (2.4)	7 (6.3)	1,168 (1.4)	6 (3.8)
Passive smoking				
Household + Workplace	406 (2.9)	6 (5.4)	1,773 (2.1)	4 (2.5)
Household only	3,172 (22.3)	41 (36.6)	16,942 (20.1)	47 (29.6)
Workplace only	470 (3.3)	5 (4.5)	3,005 (3.6)	3 (1.9)
No exposure	10,152 (71.5)	60 (53.6)	62,710 (74.3)	105 (66.0)
Asthma status				
Yes	1,659 (11.7)	9 (8.0)	4,163 (4.9)	3 (1.9)
No	12,541 (88.3)	103 (92.0)	80,267 (95.1)	156 (98.1)
Asbestos exposure*				
Yes	793 (5.6)	5 (4.5)	4,175 (4.9)	6 (3.8)
No	13,407 (94.4)	107 (95.5)	80,255 (95.1)	153 (96.2)

PY, pack-years. NS, never-smoker, FS, former smoker, CS, current smoker. # Low education (no training, primary education, lower or pre- vocational education), medium education (general secondary education, secondary vocational or professional guiding, pre-university education), high education (higher professional or university degree) and unclassifiable (subjects with other than abovementioned education).

*Following the International Standard Classification of Occupations – ISCO-08, participants with the following job codes 1323, 1324, 2142, 2144, 2145, 2146, 3131, 3139, 3151, 4110, 4321, 5411, 6222, 7124, 7126, 7212, 7213, 7231, 7411, 8111, 8112, 8114, 8182, 9311, 9321 and 9329 were considered as exposure to asbestos

427 **Table 2** Hazard ratios for the association between airflow limitation (severity) and lung cancer

Lung function	No. of participants	Person-years	No. of LC cases	LC incidence	HR (95% CI)		
Airflow limitation (binary)					Model 1	Model 2	Model 3
No	84,430	818,564	159	0.2%	ref	ref	ref
Yes	14 200	134,626	112	0.8%	2.5 (2.0-3.3)	1.7 (1.3-2.2)	1.7 (1.4-2.3)
Airflow limitation (ordinary)					Model 1	Model 2	Model 3
No	84,430	818,564	159	0.2%	ref	ref	ref
Mild	9,328	88,622	59	0.6%	2.0 (1.4-2.6)$^{\$}$	1.5 (1.1-2.0)$^{\$}$	1.5 (1.1-2.1)$^{\$}$
Moderate	4,653	44,085	47	1.0%	3.6 (2.6-5.0)$^{\$}$	2.0 (1.4-2.8)$^{\$}$	2.1 (1.5-2.9)$^{\$}$
Severe and more	219	1,919	6	2.7%	8.0 (3.5-18.2)$^{\$}$	3.6 (1.6-8.2)$^{\$}$	3.7 (1.6-8.5)$^{\$}$

428 HR, hazard ratio. CI, confidence interval. LC, lung cancer.
429 Airflow limitation: FEV1/FVC ratio < 0.7. Mild: FEV1 % predicted >80%; moderate: FEV1 % predicted = 50–79%;
430 severe: FEV1 % predicted = 30–49%; very severe: FEV1 % predicted < 30%.
431 Model 1: Cox regression model with age as time scale.
432 Model 2: Model 1 + adjusting for smoking status and pack-years.
433 Model 3: Model 2 + adjusting for sex, education, passive smoking, asthma, asbestos exposure.
434 $^{\$}$ $P_{trend} < 0.001$ in all the three models.

Table 3 Hazard ratio for airflow limitation and risk of histology-specific lung cancer

Histological type of lung cancer	Normal lung function	Airflow limitation	HR (95% CI)	
			Model 1	Model 2
No lung cancer	84271	15224	ref	ref
Adenocarcinoma	88	55	2.4 (1.7-3.4)	1.8 (1.2-2.5)
Squamous cell carcinoma	25	33	4.0 (2.4-6.8)	2.3 (1.4-4.0)
SCLC	19	9	1.7 (0.7-3.7)	1.0 (0.4-2.3)
Other	27	15	2.1 (1.1-4.0)	1.4 (0.7-2.8)

HR, hazard ratio. CI, confidence interval. SCLC, Small cell lung carcinoma,
Other: Including non-small cell lung carcinoma not otherwise specified, neuroendocrine carcinomas, adenosquamous carcinoma, sarcomatoid carcinomas, carcinoma in situ, acinic cell carcinoma.
Model 1: Cox regression model with age as time scale.
Model 2: Model 1 + adjusting for sex, smoking status and pack-years.

Table 4 Hazard ratio for airflow limitation and lung cancer risk in a lung cancer screening eligible population (n=4,009)

Lung function	No. of participants	Person-years	No. of LC cases	LC incidence	HR (95% CI)		
Airflow limitation (binary)					Model 1	Model 2	Model 3
No	2,241	20,865	24	1.1%	ref	ref	ref
Yes	1,768	16,065	44	2.5%	2.1 (1.3-3.5)	2.0 (1.2-3.3)	2.0 (1.2-3.3)
Airflow limitation (ordinal)					Model 1	Model 2	Model 3
No	2,241	20,865	24	1.1%	ref	ref	ref
Mild	939	8,573	22	2.3%	2.0 (1.1-3.6)	1.9 (1.0-3.4)	1.9 (1.1-3.4)
Moderate and more*	833	7,492	22	2.6%	2.3 (1.3-4.1)	2.1 (1.1-3.7)	2.1 (1.2-3.8)

HR, hazard ratio. CI, confidence interval. LC, lung cancer.
Airflow limitation: FEV1/FVC ratio < 0.7. Mild: FEV1 % predicted >80%; moderate: FEV1 % predicted = 50–79%; severe: FEV1 % predicted = 30–49%; very severe: FEV1 % predicted < 30%.
*Combined category because of a single lung cancer case in the "severe and more" category.
Model 1: Cox regression model with age as time scale.
Model 2: Model 1 + adjusting for smoking status and pack-years.
Model 3: Model 2 + adjusting for sex, education, passive smoking, asthma, asbestos exposure

Table 5 Effect modification by smoking status of the association between airflow limitation and lung cancer risk

Smoking status	Normal lung function			Airflow limitation			Within strata of smoking status	
	N with/with-out LC	HR (95%CI)[a]	*P* value[a]	N with/with-out LC	HR (95%CI)[b]	*P* value[b]	HR (95%CI)[c]	*P* value[c]
Never smokers	37/41 101	1.0	-	6/4286	0.9 (0.4-2.1)	0.741	0.9 (0.4-2.1)	0.741
Former smokers	64/26 705	1.6 (1.1-2.4)	0.021	46/5536	3.5 (2.3-5.5)	< 0.001	2.1 (1.4-3.2)	< 0.001
Current smokers	58/16 465	3.9 (2.6-6.0)	< 0.001	60/4266	8.4 (5.5-12.9)	< 0.001	2.2 (1.5-3.2)	< 0.001

[a] HRs and P values are presented for former/current smokers with normal lung function vs never smokers with normal lung function.
[b] HRs and P values are presented for never/former/current smokers with airflow limitation vs never smokers with normal lung function.
[c] HRs and P values are presented for airflow limitation vs normal lung function in the strata of each smoking status (never/former/current smokers).
HR was adjusted for sex, education, passive smoking, asthma and asbestos exposure with age as time scale.
Measure of effect modification on additive scale: RERI=2.1 (95%CI: 0.7-3.4) for former smokers and 4.6 (95%CI: 1.8-7.4) for current smokers.
Measure of effect modification on multiplicative scale: Ratio of HRs=2.5 (95%CI: 1.0-6.5) for former smokers and 2.5 (95%CI: 1.0-6.3) for current smokers.

Figure legends

Figure 1 Flowchart of participants inclusion