Airflow Limitation Increases Lung Cancer Risk in Smokers: The Lifelines Cohort Study

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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.

Introduction

Both chronic obstructive pulmonary disease (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 article (15). The adult population recruited

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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for Lifelines study is broadly representative for the adult population of the north of the Netherlands (16). For this 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 (i) participants with technically invalid spirometry data, (ii) participants with prevalent or prior history of lung cancer, (iii) participants with missing values in any of the included covariates (see **Fig. 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

Prebronchodilator 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% to 79%; GOLD III (severe): FEV1% predicted = 30% to 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 January 26, 2021. After linkage, an expert pulmonary pathologist reviewed all diagnoses regarding lung cancer. The conclusion of primary lung cancer was concluded from the pathologic 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 (January 26, 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 histologic type of lung cancer were also fitted. Due to small numbers these models were adjusted for sex, and smoking status and pack-years only. 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 [$RERI = HR_{11}\text{-}HR_{10}\text{-}HR_{01}+1$; ratio of $HRs = HR_{11}/(HR_{10}{}^{*}HR_{01})$; ref. 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 (Supplementary 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%

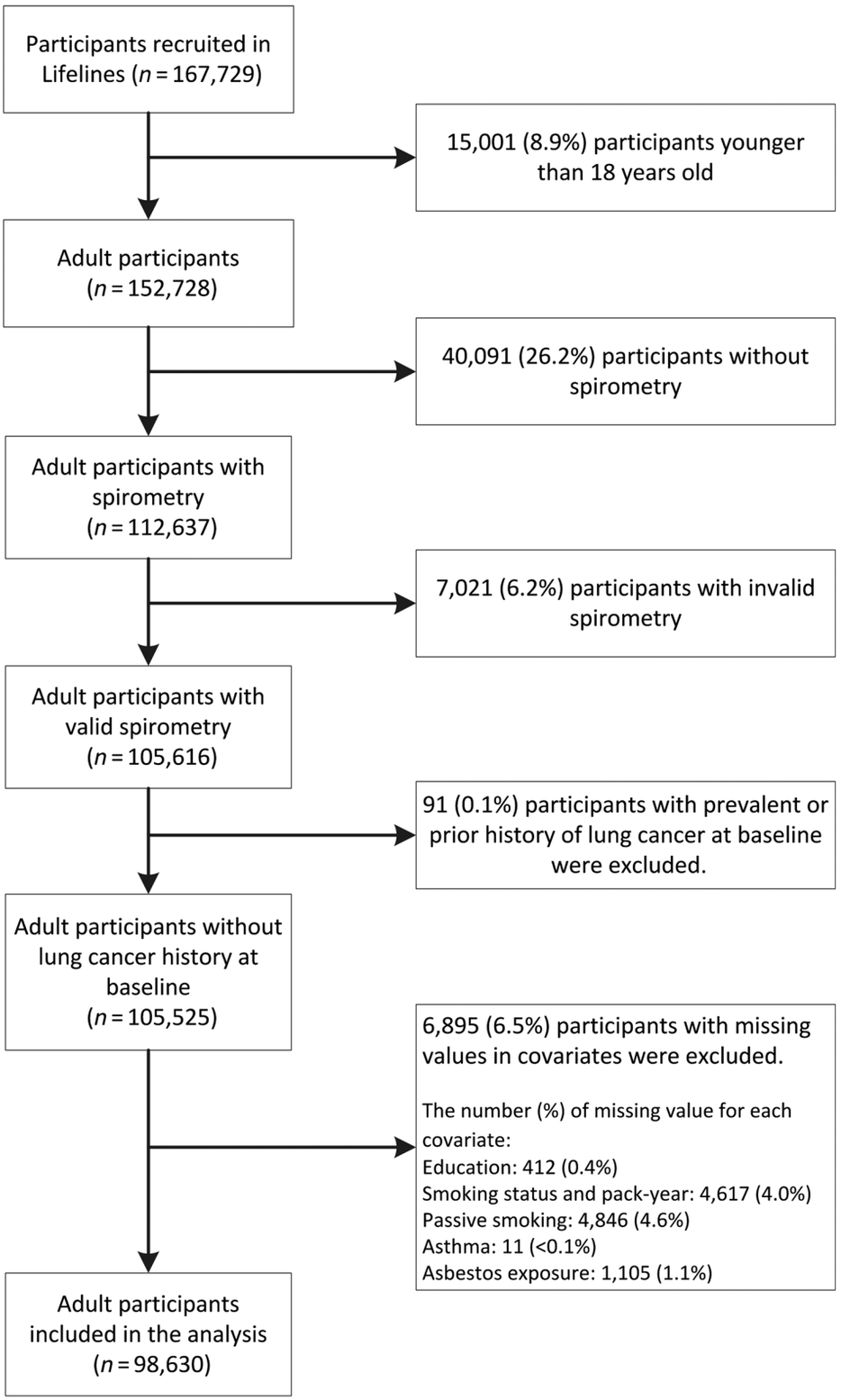

Figure 1.
Flowchart of participants' inclusion.

(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 (Supplementary 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 Supplementary Fig. S1. The characteristics of included participants and lung cancer cases by smoking status are presented in Supplementary 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 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, 1.6–8.5),

Table 1. Baseline characteristics of study participants by airflow limitation status.

	Airflow limitation (n = 14,200)		Normal lung function (n = 84,430)	
Baseline characteristics	**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[a]				
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[b]				
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)

Abbreviations: CS, current smoker; FS, former smoker; NS, never-smoker; PY, pack-years.

[a]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 above-mentioned education).

[b]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.

Table 2. HRs 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)[a]	1.5 (1.1–2.0)[a]	1.5 (1.1–2.1)[a]
Moderate	4,653	44,085	47	1.0%	3.6 (2.6–5.0)[a]	2.0 (1.4–2.8)[a]	2.1 (1.5–2.9)[a]
Severe and more	219	1,919	6	2.7%	8.0 (3.5–18.2)[a]	3.6 (1.6–8.2)[a]	3.7 (1.6–8.5)[a]

Note: 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%. 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.
Abbreviation: LC, lung cancer.
[a]P_{trend} < 0.001 in all the three models.

respectively (P_{trend} < 0.001; **Table 2**). When analyzed by histological subtype of lung cancer, airflow limitation was associated with an increased risk of both adenocarcinoma (1.8; 95% CI, 1.2–2.5) and squamous cell carcinoma (2.3; 95% CI, 1.4–4.0; **Table 3**).

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

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

The multivariable analysis showed that the HR for the association between airflow limitation and 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, 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 former smokers and 4.6 (95% CI, 1.8–7.4) for current smokers, which means that there was positive effect modification by smoking status of the association between airflow limitation and lung cancer risk on an additive scale. On a multiplicative scale, the ratio of HRs was 2.5 (95% CI, 1.0–6.5) for former smokers and 2.5 (95% CI, 1.0–6.3) for current smokers, which means that the estimated effect of airflow limitation on the HR scale in the presence of current/former smoking was larger than the estimated effect of airflow limitation in the absence of smoking.

Sensitivity analysis

The GLI-defined airflow limitation was associated with an increased risk of lung cancer, with the adjusted HR of 1.7 (95% CI, 1.3–2.3). The analysis in the subset of participants aged ≥ 50 years showed the adjusted HR of 1.8 (95% CI, 1.3–2.4; Supplementary 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 with 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 (6/219).

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

Table 3. HR for airflow limitation and risk of histology-specific lung cancer.

Histologic type of lung cancer	Normal lung function	Airflow limitation	HR (95% CI)	
			Model 1	Model 2
No lung cancer	84,271	15,224	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)

Note: 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.
Abbreviation: SCLC, Small cell lung carcinoma.

Table 4. HR 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[a]	833	7,492	22	2.6%	2.3 (1.3–4.1)	2.1 (1.1–3.7)	2.1 (1.2–3.8)

Note: 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%. 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.
Abbreviation: LC, lung cancer.
[a]Combined category because of a single lung cancer case in the "severe and more" category.

caused by small airway narrowing (chronic bronchitis) and destruction of lung parenchyma (emphysema), which is 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; ref. 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; ref. 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

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

	Normal lung function			Airflow limitation			Within strata of smoking status	
Smoking status	*N* with/with-out LC	HR (95% CI)[a]	*P*[a]	*N* with/with-out LC	HR (95% CI)[b]	*P*[b]	HR (95% CI)[c]	*P*[c]
Never smokers	37/41 101	1.0	—	6/4,286	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	46/5,536	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	60/4,266	8.4 (5.5–12.9)	<0.001	2.2 (1.5–3.2)	<0.001

Note: 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.
[a]HRs and *P* values are presented for former/current smokers with normal lung function versus never smokers with normal lung function.
[b]HRs and *P* values are presented for never/former/current smokers with airflow limitation versus never smokers with normal lung function.
[c]HRs and *P* values are presented for airflow limitation versus normal lung function in the strata of each smoking status (never/former/current smokers).

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 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.

Authors' Disclosures

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Authors' Contributions

Y. Du: Conceptualization, software, formal analysis, visualization, methodology, writing–original draft. **G. Sidorenkov:** Conceptualization, supervision, methodology, writing–original draft, writing–review and editing. **H.J.M. Groen:** Conceptualization, visualization, methodology, writing–review and editing. **M.A. Heuvelmans:** Validation, visualization, methodology, writing–review and editing. **R. Vliegenthart:** Conceptualization, investigation, methodology, writing–review and editing. **M.D. Dorrius:** Validation, investigation, writing–review and editing. **W. Timens:** Conceptualization, data curation, methodology, writing–original draft, writing–review and editing. **G.H. de Bock:** Conceptualization, resources, supervision, funding acquisition, methodology, writing–original draft, project administration, writing–review and editing.

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