[Thoracic Oncology Original Research]

CHEST

Rapid FEV_1 Decline and Lung Cancer Incidence in South Korea

Hyun Woo Lee, MD; Hyo-Jin Lee, MD; Jung-Kyu Lee, MD; Tae Yeon Park, MD; Eun Young Heo, MD; and Deog Kyeom Kim, MD

BACKGROUND: Impaired lung function is associated with a higher risk of developing lung cancer. However, lung function is a dynamic variable and must be evaluated longitudinally. This study reports on the relationship between accelerated lung function decline and development of lung cancer.

RESEARCH QUESTION: Is accelerated lung function decline associated with the development of lung cancer?

STUDY DESIGN AND METHODS: A longitudinal, observational study was performed by using epidemiologic data from two population-based studies comprising subjects assessed biannually from 2001 to 2019 in South Korea. Eligible subjects were between 40 and 69 years of age and were followed up by using spirometry. Spirometry measurements were made at each follow-up. Patients with a decline in $FEV_1 > 60$ mL per year were defined as rapid FEV_1 decliners. The relationship between lung cancer and rapid FEV_1 decline was evaluated by using adjusted Cox regression models with covariates, including age, sex, smoking history, FEV_1/FVC, and WBC count.

RESULTS: Among the 8,549 eligible subjects, 1,287 (15.1%) had rapid FEV_1 decline, and 48 (0.6%) had newly developed lung cancer. The risk of lung cancer development was increased in the subjects aged ≥ 45 years and those with ≥ 30 pack-years of smoking, low baseline FEV_1/FVC, low forced expiratory flow between 25% and 75% of vital capacity, rapid FEV_1 decline, and increased WBC count. Rapid FEV_1 decline was an independent risk factor for lung cancer development (adjusted hazard ratio, 2.44; 95% CI, 1.30-4.57; $P = .006$). Time-dependent net reclassification improvement showed a benefit of FEV_1 decline rate in determining subjects at risk of lung cancer when added to conventional practice (categorical, 0.32 [95% CI, 0.00-0.64]; continuous, 0.83 [95% CI, 0.14-1.25]).

INTERPRETATION: The FEV_1 decline rate may be a potential biomarker for lung cancer development. Further study is needed to identify whether patients with rapid FEV_1 decline warrant lung cancer assessment or screening. CHEST 2022; ■(■):■-■

KEY WORDS: cohort studies; FEV; lung cancer; respiratory function tests; risk factors

ABBREVIATIONS: FEF_{25-75} = forced expiratory flow between 25% and 75% of vital capacity; mNLST = modified National Lung Screening Trial; mNLST-D = combined modified National Lung Screening Trial criteria and FEV_1 decline rate; NLST = National Lung Screening Trial; NRI = net reclassification improvement

AFFILIATIONS: From the Division of Pulmonary and Critical Care, Department of Internal Medicine, Seoul Metropolitan Government-Seoul National University Boramae Medical Center, Seoul, South Korea.

FUNDING/SUPPORT: The authors have reported to *CHEST* that no funding was received for this study.

CORRESPONDENCE TO: Hyun Woo Lee, M.D; email: athrunzara86@snu.ac.kr; athrunzara86@gmail.com

DOI: https://doi.org/10.1016/j.chest.2022.03.018

FLA 5.6.0 DTD ■ CHEST4978_proof ■ 26 April 2022 ■ 1:39 pm ■ EO: CHEST-21-3489

Take-home Points

Study Question: Is rapid FEV_1 decline (annual FEV_1 decline rate > 60 mL per year) an independent risk factor for lung cancer development in the general population?

Results: Rapid FEV_1 decliners showed a significantly higher hazard of lung cancer development than nonrapid FEV_1 decliners.

Interpretation: In the general population, the FEV_1 decline rate is a potential biomarker for lung cancer development and may improve accuracy of conventional lung cancer screening.

Internationally, lung cancer is the second most commonly diagnosed malignancy and was the leading cause of cancer-related deaths in 2020.[1] The development of lung cancer is intricately influenced by sociodemographic, environmental, clinical, and genetic factors.[2] Among clinically important factors related to lung cancer, lung function has been evaluated as a potentially useful biomarker for the diagnosis or prognosis of lung cancer.[3-5]

Previous studies have reported that a lower FEV_1 or airflow limitation is related to a higher risk of lung cancer development. The risk of lung cancer is higher in patients with a higher severity of airflow limitation.[6] The incidence of lung cancer is reportedly higher in patients with obstructive airway diseases, including COPD, emphysema, and asthma.[7-10] Systematic reviews and meta-analyses have shown a strong association between reduced FEV_1 and lung cancer.[5,11] The association between lung function impairment and a higher risk of lung cancer can be explained by cigarette smoking, which, as a mediator, aggravates the FEV_1 decline rate and increases lung cancer risk.[12] In addition, cigarette smoking causes COPD, another independent risk factor for lung cancer.[13] However, even after controlling for smoking history, reduced FEV_1 was still found to be an independent risk factor for lung cancer in both current and ex-smokers.[14] Impaired lung function and lung cancer may share genetic susceptibility[15] or pathophysiological mechanisms, including impaired clearance of carcinogens and dysregulation of reactive oxygen species.[16,17]

Lung function is a dynamic variable that changes with aging, health behavior, or environmental factors. Therefore, to identify the relationship between lung function and lung cancer development, the longitudinal changes rather than fixed baseline values of lung function must be evaluated. We longitudinally observed and estimated annual FEV_1 declines and investigated whether rapid FEV_1 decline is an independent risk factor for lung cancer development in the general population.

Study Design and Methods

We followed the Strengthening the Reporting of Observational Studies in Epidemiology statement to report the current study.[18]

Study Design and Eligibility Criteria

This longitudinal, observational study was designed by using epidemiologic data in South Korea obtained from two population-based studies (the rural Ansung and urban Ansan cohorts) as part of the Korean Genome Epidemiology Study (KoGES). This project recruited the general population between 40 and 69 years of age and followed them up biannually from 2001 to 2019. The methodologic information of the rural Ansung and urban Ansan cohorts has been described in a previous cohort profile report.[19] The eligibility criteria were as follows: (1) no lung cancer history at baseline questionnaire administration; (2) no suspicious lung cancer lesion at baseline chest radiograph; (3) underwent spirometry at baseline examination; and (4) subsequent follow-up with spirometry prior to diagnosis of lung cancer. Patients with missing data on smoking history or chronic lung disease at baseline were excluded from the study.

Variables and Outcomes

At baseline assessment, sociodemographic and anthropometric information was obtained, including age, sex, BMI, waist circumference, smoking history and pack-years of smoking, exercise and education history, and income. Baseline medical information, including underlying comorbid diseases and medication history, was acquired by using several questionnaires. For baseline spirometric assessment, we obtained pre-bronchodilator FEV_1 and FVC (in liters and percentage of the predicted value), FEV_1/FVC, and forced expiratory flow between 25% and 75% of vital capacity (FEF_{25-75}) (in liters and percentage of the predicted value). Laboratory test results were acquired to evaluate baseline general medical conditions. A protocolized and systematic questionnaire was used to identify patients with newly developed malignancies at each follow-up. Patients who reported newly developed lung cancer, as diagnosed by physicians, were investigated further.

Spirometric Data

We estimated the annual FEV_1 decline (in milliliters per year) for each subject. A linear model of FEV_1 and years since baseline was fitted for each subject using all individual spirometric data from baseline to end of follow-up. The slope of the resulting linear model represents the subject's annual rate of FEV_1 change (in milliliters per year).[20,21] Follow-up was terminated by diagnosis of lung cancer, death, or censoring. After the linear model was fitted in each individual, annual FEV_1 change was graphically depicted. Detailed information is provided in e-Table 1.

The included subjects were classified into two groups based on the annual FEV_1 decline rate: the group with annual FEV_1 decline rate > 60 mL per year (defined as rapid FEV_1 decliners) and the group

FLA 5.6.0 DTD ■ CHEST4978_proof ■ 26 April 2022 ■ 1:39 pm ■ EO: CHEST-21-3489

with annual FEV_1 decline rate ≤ 60 mL per year (defined as nonrapid FEV_1 decliners). These definitions were based on the current operational definition of accelerated FEV_1 decline.[22]

Net Reclassification Improvement

We investigated whether adding FEV_1 decline rate to the National Lung Screening Trial (NLST) criteria better identifies subjects at high risk for lung cancer. Because the cohort data lacked information regarding the duration of smoking cessation, we created modified NLST (mNLST) criteria to determine subjects at high risk for lung cancer. The mNLST criteria are as follows: (1) age ≥ 55 years and < 70 years; (2) current smoker or ex-smoker; and (3) ≥ 30 pack-years of smoking. Our suggested new criteria that combine mNLST criteria and FEV_1 decline rate (mNLST-D) to identify subjects at high risk for lung cancer were: (1) high risk based on the mNLST criteria; or 2) FEV_1 decline rate > 60 mL per year. To compare the accuracy between the mNLST and the mNLST-D criteria, categorical or continuous time dependent net reclassification improvement (NRI) was estimated.[23]

Statistics

Continuous variables were analyzed with the Student *t* test or the Wilcoxon rank sum test, and categorical variables were analyzed by using the χ^2 test or Fisher's exact test. The Cochran-Armitage test for trend was conducted to evaluate lung cancer incidence across quintiles. Univariate and multivariate analyses with the Cox proportional hazards model were conducted to identify whether rapid FEV_1 decline is an independent risk factor for lung cancer development. For the multivariable model, we included the variables with a statistically significant relationship with lung cancer development in each univariable model. In addition, sex was included as a variable for the multivariable model, as sex differences in lung function have been well verified.[24] The variance inflation factor for significant multicollinearity was > 4.0. We estimated categorical and continuous time dependent NRI and 95% CIs to compare two types of risk prediction models based on time-to-event data using the R package "nricens." The *P* value for statistical significance was set at < .05. R statistical software version 4.1.0 (R Core Team [2020]) was used for all statistical analyses.

Ethics

The current study adhered to the principles of the Declaration of Helsinki. The Korean Centers for Disease Control and Prevention obtained written informed consent from all patients included in the study. Ethical approval for the current study was obtained from the Institutional Review Board Committee of Seoul National University Seoul Metropolitan Government (SNU-SMG) Boramae Medical Center (IRB No. 07-2021-24).

Results

Of the total of 10,030 subjects, 9,885 had no history of lung cancer or no suspicious lung cancer lesion on baseline chest radiograph. Baseline lung function was measured in 9,638 subjects, and follow-up lung function was measured prior to the diagnosis of lung cancer in 8,713 subjects. Among the eligible 8,713 subjects, we excluded 160 subjects with no data on smoking history and 4 subjects with no data on history of chronic lung disease. Ultimately, 8,549 subjects were included in the current study (e-Fig 1).

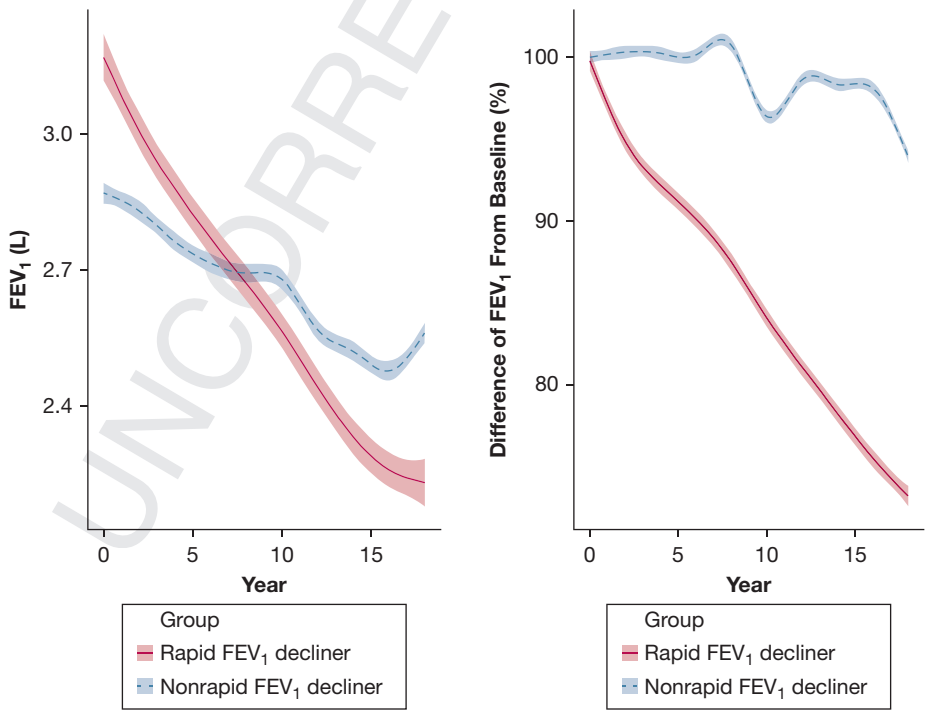

Figure 1 – *Annual FEV_1 decline from baseline lung function. Annual FEV_1 decline is graphically compared between rapid FEV_1 decliners and nonrapid FEV_1 decliners. Lines represent the mean value of FEV_1, and the shaded regions represent the SE of FEV_1.*

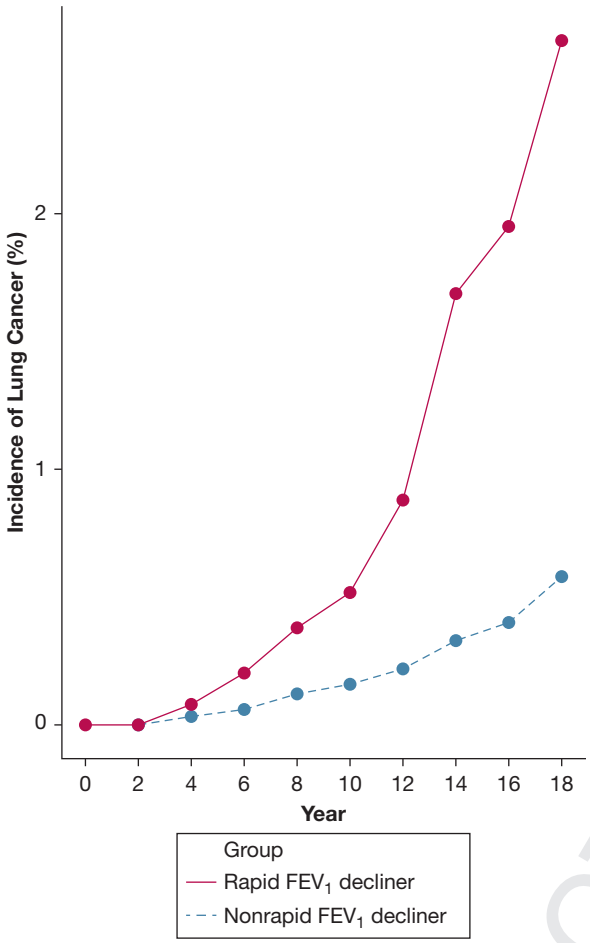

Figure 2 – *Cumulative lung cancer incidence rate measured at 2-year intervals. Cumulative lung cancer incidence rate is graphically compared between rapid FEV_1 decliners and nonrapid FEV_1 decliners.*

During the follow-up, FEV_1 was measured a median of seven times (interquartile range, 4-8) in each patient, and the median annual FEV_1 decline rate was 37.2 mL per year (interquartile range, 26.7-50.0 mL per year) (e-Fig 2). Among the eligible 8,549 subjects, 1,287 (15.1%) subjects met the definition for rapid FEV_1 decliners, and the other 7,262 (84.9%) subjects were classified as nonrapid FEV_1 decliners. Rapid FEV_1 decliners annually lost 76.8 mL and 2.6% of FEV_1 relative to their baseline lung function, whereas nonrapid FEV_1 decliners annually lost 28.0 mL and 1.0% of FEV_1 relative to their baseline lung function (Fig 1).

Baseline Characteristics and Clinical Features

At baseline, rapid FEV_1 decliners were older, comprised more men, had a lower BMI but a larger waist circumference, and reported more cigarette smoking exposure (Table 1). In terms of socioeconomic status, rapid FEV_1 decliners exercised less, were less educated, and had less income. There was no significant difference in underlying comorbid diseases and medication history between the rapid and nonrapid FEV_1 decliners. In the baseline spirometric assessment, rapid FEV_1 decliners exhibited higher FEV_1 or FVC and a lower FEV_1/FVC than the nonrapid FEV_1 decliners (Table 2). There were significant differences in laboratory findings between the two groups. Inflammatory markers, including WBC and high-sensitivity C-reactive protein, were significantly elevated in rapid FEV_1 decliners.

Risk of Lung Cancer Development

During the follow-up period, the cumulative rate of lung cancer development was significantly higher in rapid FEV_1 decliners than in nonrapid FEV_1 decliners ($P < .001$) (Fig 2). Lung cancer incidence linearly increased with accelerated FEV_1 decline (Cochran-Armitage test for trend, $P = .005$) (e-Fig 3). We summarized the unadjusted hazard ratios for lung cancer development according to the different variables in baseline characteristics and clinical features (e-Tables 2, 3). Among the evaluated variables, age $\geq$ 45 years, $\geq$ 30 pack-years of smoking, low baseline FEV_1/FVC, low FEF_{25-75}, annual FEV_1 decline rate $>$ 60 mL per year, and increased WBC count were related to an increased risk of lung cancer development (Table 3). Following multivariable adjustment, we found that an annual FEV_1 decline rate $>$ 60 mL per year was independently associated with lung cancer development (adjusted hazard ratio, 2.44; 95% CI, 1.30-4.57; $P = .006$).

Net Reclassification Improvement

A reclassification table for development of lung cancer was summarized according to mNLST criteria and mNLST-D criteria (e-Table 4). Categorical time-dependent NRI at 18 years was 0.32 (95% CI, 0.00-0.64) and continuous time-dependent NRI at 18 years was 0.83 (95% CI, 0.14-1.25).

Discussion

In this longitudinal observational study, we found a significant association between lung function change and lung cancer development in a large, community-based general population. During the 18 years of observation, 15% of the general population had a FEV_1 decline rate $>$ 60 mL per year. Forty-eight cases of lung cancer developed in the eligible 8,549 subjects, and the crude incidence rate was calculated as 35.1 per 100,000 person-years, which is close to the estimated crude incidence rate (41-42 per 100,000 person-years) of lung

FLA 5.6.0 DTD ■ CHEST4978_proof ■ 26 April 2022 ■ 1:39 pm ■ EO: CHEST-21-3489

TABLE 1] Baseline Characteristics of Rapid and Nonrapid FEV_1 Decliners

Characteristic	Nonrapid FEV_1 Decliner (n = 7,262)	Rapid FEV_1 Decliner (n = 1,287)	*P* Value
Age, y	51.4 ± 8.6	54.7 ± 9.2	< .001
Male	3,226 (44.4)	890 (69.2)	< .001
BMI, kg/cm^2	24.7 ± 3.1	24.1 ± 3.2	< .001
Waist circumference, cm	82.6 ± 8.7	83.7 ± 8.6	< .001
Smoking history			
Never smoker	4,580 (63.1)	514 (39.9)	< .001
Ex-smoker	1,106 (15.2)	242 (18.8)	< .001
Current smoker	1,576 (21.7)	531 (41.3)	< .001
≥ 30 pack-years	718 (9.9)	310 (24.1)	< .001
Exercise history ≥ 2 per week	2,228 (30.7)	318 (24.7)	< .001
Education history ≥ 12 y	1,092 (15.0)	137 (10.6)	< .001
Income[a]			
< 873 dollars per month	2,294 (32.1)	551 (43.4)	< .001
873-1,745 dollars per month	2,137 (29.4)	365 (28.4)	.458
1,746 ≥ dollars per month	2,717 (37.4)	353 (27.4)	< .001
Underlying comorbid disease			
Chronic lung disease	183 (2.5)	31 (2.4)	.890
Cardiovascular disease	103 (1.4)	20 (1.6)	.803
Congestive heart failure	19 (0.3)	3 (0.2)	1.000
Hypertension	1,228 (16.9)	226 (17.6)	.595
Diabetes	1,997 (27.5)	329 (25.6)	.160
Dyslipidemia	2,105 (29.0)	380 (29.5)	.728
Dementia	2 (0.0)	1 (0.1)	.938
Cerebrovascular disease	59 (0.8)	18 (1.4)	.059
Medication history			
Oral corticosteroid	19 (0.3)	2 (0.2)	.686
Treatment for asthma	53 (0.7)	10 (0.8)	.996

Data are presented as mean ± SD or No. (%).
[a]Conversion: 1000 won is converted into 0.873 dollar.

cancer in South Korea from 1999 to 2017.[25] More cases of newly developed lung cancers were noted among the rapid FEV_1 decliners group. A rapid FEV_1 decline was related to a significantly higher hazard for lung cancer development in the multivariable Cox regression model. Considering time-dependent NRIs at 18 years, the FEV_1 decline rate may be a potential biomarker for lung cancer screening.

The association between lung function and lung cancer has been investigated internationally. In the United States, prospective studies clarified the significant relationship between COPD and lung cancer development.[8,26] This relationship was evident in high-risk populations, including asbestos-exposed heavy smokers[27] and construction workers.[6] In particular, FEV_1 < 80% with airway obstruction was reported as an independent risk factor for lung cancer development among the 5,402 subjects who participated in a National Health and Nutrition Examination Survey.[7] A cohort study in Italy showed that FEV_1 < 90% was related to lung cancer development in 3,806 heavy smokers, regardless of COPD status.[14] In the United Kingdom, performance of a lung cancer prediction model for never smokers improved following the addition of lung function as a covariable.[28] A systematic review and meta-analysis concluded that low FEV_1 is strongly associated with lung cancer.[11] However, previous studies were mostly conducted in Western countries, and only baseline lung function data were evaluated in those studies. Compared with previous studies, the current study was conducted in the South Korean general

FLA 5.6.0 DTD ■ CHEST4978_proof ■ 26 April 2022 ■ 1:39 pm ■ EO: CHEST-21-3489

TABLE 2] Spirometric and Laboratory Findings at Initial Assessment

Variable	Nonrapid FEV_1 Decliner (n = 7,262)	Rapid FEV_1 Decliner (n = 1,287)	*P* Value
Spirometry			
FEV_1, L	2.87 ± 0.67	3.19 ± 0.78	< .001
FEV_1, % of the predicted value	111.4 ± 16.9	116.9 ± 18.7	< .001
FVC, L	3.59 ± 0.86	4.09 ± 0.95	< .001
FVC, % of the predicted value	104.2 ± 14.2	110.5 ± 14.9	< .001
FEV_1/FVC	80.3 ± 7.4	78.2 ± 8.1	< .001
FEF_{25-75}, L	3.05 ± 2.19	3.11 ± 1.26	.431
FEF_{25-75}, %	103.1 ± 32.7	104.2 ± 36.1	.312
Blood test			
WBC, /μL[b]	6,490 ± 1,770	6,680 ± 1,880	< .001
Hemoglobin, g/dL	13.5 ± 1.6	14.0 ± 1.4	< .001
Platelet, 10^3/μL	266 ± 63	262 ± 64	.036
hs-CRP, mg/L	0.14 (0.06-0.24)	0.16 (0.09-0.26)	.008
AST, IU/L	25.0 (21.0-30.0)	25.0 (21.0-31.0)	.032
ALT, IU/L	21.4 (16.1-30.0)	22.0 (16.1-31.0)	.094
GGT, IU/L	19.0 (13.0-35.0)	24.0 (15.0-45.2)	< .001
Total protein, g/dL	6.1 ± 1.4	6.3 ± 1.3	< .001
Albumin, g/dL	4.3 ± 0.4	4.4 ± 0.4	.003
BUN, mg/dL	14.2 ± 3.6	14.4 ± 3.8	.094
Creatinine, mg/dL	0.83 ± 0.20	0.85 ± 0.20	.002
Total cholesterol, mg/dL	194.5 ± 35.4	191.1 ± 36.7	.002
HDL cholesterol, mg/dL	46.1 ± 10.6	47.2 ± 11.6	< .001
LDL cholesterol, mg/dL	119.9 ± 34.0	115.4 ± 39.1	< .001
Triglyceride, mg/dL	156.7 ± 97.2	164.7 ± 117.9	.008

Data are expressed as mean ± SD, median (interquartile range), or number (percentage). ALT = alanine aminotransferase; AST = aspartate aminotransferase; FEF_{25-75} = forced expiratory flow between 25% and 75% of vital capacity; GGT = gamma-glutamyl transpeptidase; HDL = high-density lipoprotein; hs-CRP = high-sensitivity C-reactive protein; LDL = low-density lipoprotein.

population and revealed the association between lung cancer development and dynamic changes in lung function, rather than baseline lung function.

Lung cancer development and accelerated FEV_1 decline rate may share common pathogenic mechanisms for chronic airway inflammation and genetic alterations.[29,30] Previous studies have reported that smoking or environmental exposure may induce the production of pro-inflammatory cytokines that provoke airway inflammation and increase the risk of lung cancer development.[31] Single nucleotide polymorphisms in inflammatory cytokine genes, including IL-1A and IL-1B polymorphisms, are associated with an elevated risk of lung cancer.[32] Cigarette smoking can activate nuclear factor kappa B, an important cytokine in lung inflammation and lung carcinogenesis.[33,34] In addition, chronic exposure to reactive oxygen species can induce chronic airway inflammation, DNA alteration, and lung cancer development.[35] Airway inflammation with impaired lung function in conjunction with *KRAS* mutation has been shown to increase the risk of lung cancer through the tumor-promoting functions of hypoxia-inducible factor-1.[36] It is therefore speculated that the FEV_1 decline rate may be an environmental biomarker for exposure to carcinogens,[14] or a genetic biomarker for susceptibility to carcinogens.[37] To verify the utility of FEV_1 decline rate as an auxiliary biomarker for lung cancer screening, the inflammatory pathway or the gene expression profiles related to FEV_1 change need to be further investigated.

Our multivariable analysis showed that the FEV_1 decline rate may be an independent biomarker for lung cancer, regardless of baseline lung function impairment. The natural course of lung function change has been reported to be heterogeneous and difficult to predict based on baseline conditions.[38] Indeed, impaired

FLA 5.6.0 DTD ■ CHEST4978_proof ■ 26 April 2022 ■ 1:39 pm ■ EO: CHEST-21-3489

TABLE 3] Independent Risk Factors for Lung Cancer Development

Variable	Univariable Analysis		Multivariable Analysis	
	Hazard Ratio	*P* Value	Hazard Ratio	*P* Value
Age ≥ 45 y	2.87 (1.29-6.39)	.010	2.30 (1.01-5.22)	.047
Male	1.42 (0.80-1.24)	.226	1.78 (0.88-3.62)	.110
≥ 30 pack-years of smoking	3.63 (2.04-6.45)	< .001	2.44 (1.30-4.57)	.006
FEV_1/FVC, %	0.96 (0.93-0.99)	.004	0.97 (0.94-1.01)	.126
FEF_{25-75}, %	0.99 (0.98-1.00)	.044	...	...
FEV_1 decline rate > 60 mL per year	3.40 (1.88-6.13)	< .001	2.34 (1.28-4.28)	.006
WBC, /μL	1.17 (1.03-1.32)	.014	1.13 (0.99-1.28)	.068

Forced expiratory flow between 25% and 75% of vital capacity (FEF_{25-75}) percentage was not included in this multivariable analysis due to multicollinearity with FEV_1/FVC percentage.

baseline FEV_1 was not necessarily related to subsequent changes in FEV_1.[39] Therefore, the FEV_1 decline rate has recently been studied as a potential biomarker that provides additional information on clinical outcomes such as health status and exacerbation rate.[40] Moreover, since the acceleration of FEV_1 decline has already occurred prior to the detection of lung function impairment,[41] individual risk evaluation is necessary even in patients in the pre-COPD stage.[42] The current study suggests that even subjects without comorbid chronic lung disease may have a high risk of lung cancer if the FEV_1 decline rate is accelerated.

The current study has several limitations. First, we could not specify which histologic type of lung cancer was more related to lung function decline because there was no available information on histologic findings. Previous studies have shown that the association between FEV_1 and lung cancer development was significant in a composite histologic type other than adenocarcinoma.[14] COPD is an independent risk factor for squamous cell carcinoma.[43] Squamous cell carcinoma of the lung originates from cellular transformation of the bronchial epithelium, which is mainly caused by environmental or occupational carcinogens such as cigarette smoking.[44] Therefore, it is speculated that the FEV_1 decline rate is associated with the development of squamous cell carcinoma. Second, occupational or environmental exposure was not analyzed as a covariable because information on individual addresses was not available. In this study, indirect indicators of occupational exposure, such as income or education history, were associated with rapid FEV_1 decline but were not significantly associated with lung cancer incidence. Third, the prevalence of underlying chronic lung disease (at 2.5%) was most likely underestimated. In the Korean population aged > 40 years, the prevalence of COPD was reported to be 13.4%.[45] In fact, approximately 9% of our study patients had FEV_1/FVC < 0.7. This finding suggests that more than one-half of the patients with chronic lung disease were unaware that they had chronic lung disease. To supplement this limitation, we included FEV_1/FVC as a variable for multivariable analysis. Fourth, a relatively small number of lung cancers limit the generalization of our results. A larger scale cohort study is needed in which the results of our study are reproduced.

Interpretation

The FEV_1 decline rate is an easily obtainable potential biomarker to detect lung cancer development. Further study is needed to identify whether rapid FEV_1 decliners benefit from lung cancer assessment or screening in general population.

FLA 5.6.0 DTD ■ CHEST4978_proof ■ 26 April 2022 ■ 1:39 pm ■ EO: CHEST-21-3489

Acknowledgments

Author contributions: H. W. L. accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish. H. W. L. was responsible for study concept and design, as well as study supervision and drafting of the manuscript; H. W. L. and H.-J. L. were responsible for acquisition of data; H. W. L., J.-K. L., and T. Y. P. analyzed and interpreted the data; and H. W. L., E. Y. H., and D. K. K. were responsible for critical revision of the manuscript and important intellectual content.

Financial/nonfinancial disclosures: None declared.

Additional information: The e-Figures and e-Tables can be found in the Supplemental Materials section of the online article.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin*. 2021;71(3):209-249.
2. Malhotra J, Malvezzi M, Negri E, La Vecchia C, Boffetta P. Risk factors for lung cancer worldwide. *Eur Respir J*. 2016;48(3):889-902.
3. Lee JH, Song EM, Sim YS, Ryu YJ, Chang JH. Forced expiratory volume in one second as a prognostic factor in advanced non-small cell lung cancer. *J Thorac Oncol*. 2011;6(2):305-309.
4. Kuller LH, Ockene J, Meilahn E, Svendsen KH. Relation of forced expiratory volume in one second (FEV1) to lung cancer mortality in the Multiple Risk Factor Intervention Trial (MRFIT). *Am J Epidemiol*. 1990;132(2):265-274.
5. Fry JS, Hamling JS, Lee PN. Systematic review with meta-analysis of the epidemiological evidence relating FEV1 decline to lung cancer risk. *BMC Cancer*. 2012;12:498.
6. 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.
7. Mannino DM, Aguayo SM, Petty TL, Redd SC. Low lung function and incident lung cancer in the United States: data from the First National Health and Nutrition Examination Survey follow-up. *Arch Intern Med*. 2003;163(12):1475-1480.
8. Skillrud DM, Offord KP, Miller RD. Higher risk of lung cancer in chronic obstructive pulmonary disease. A prospective, matched, controlled study. *Ann Intern Med*. 1986;105(4):503-507.
9. Kishi K, Gurney JW, Schroeder DR, Scanlon PD, Swensen SJ, Jett JR. The correlation of emphysema or airway obstruction with the risk of lung cancer: a matched case-controlled study. *Eur Respir J*. 2002;19(6):1093-1098.
10. Santillan AA, Camargo CA Jr, Colditz GA. A meta-analysis of asthma and risk of lung cancer (United States). *Cancer Causes Control*. 2003;14(4):327-334.
11. Wasswa-Kintu S, Gan WQ, Man SF, Pare PD, Sin DD. Relationship between reduced forced expiratory volume in one second and the risk of lung cancer: a systematic review and meta-analysis. *Thorax*. 2005;60(7):570-575.
12. Simmons MS, Connett JE, Nides MA, et al. Smoking reduction and the rate of decline in FEV(1): results from the Lung Health Study. *Eur Respir J*. 2005;25(6):1011-1017.
13. Laniado-Laborín R. Smoking and chronic obstructive pulmonary disease (COPD). Parallel epidemics of the 21 century. *Int J Environment Res Public Health*. 2009;6(1):209-224.
14. Calabrò E, Randi G, La Vecchia C, et al. Lung function predicts lung cancer risk in smokers: a tool for targeting screening programmes. *Eur Respir J*. 2010;35(1):146-151.
15. Brennan P, Hainaut P, Boffetta P. Genetics of lung-cancer susceptibility. *Lancet Oncol*. 2011;12(4):399-408.
16. Meyer MB, Luk GD, Sotelo JM, Cohen BH, Menkes HA. Hypothesis: the role of the lung in stomach carcinogenesis. *Am Review Respir Dis*. 1980;121(5):887-892.
17. Schottenfeld D, Beebe-Dimmer JL. Advances in cancer epidemiology: understanding causal mechanisms and the evidence for implementing interventions. *Ann Rev Public Health*. 2005;26:37-60.
18. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet (London, England)*. 2007;370(9596):1453-1457.
19. Kim Y, Han BG. Cohort profile: the Korean Genome and Epidemiology Study (KoGES) Consortium. *Int J Epidemiol*. 2017;46(2):e20.
20. Schlesselman JJ. Planning a longitudinal study. II. Frequency of measurement and study duration. *J Chronic Dis*. 1973;26(9):561-570.
21. Sherrill DL, Lebowitz MD, Knudson RJ, Burrows B. Continuous longitudinal regression equations for pulmonary function measures. *Eur Respir J*. 1992;5(4):452-462.
22. Martinez FJ, Han MK, Allinson JP, et al. At the root: defining and halting progression of early chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2018;197(12):1540-1551.
23. Pencina MJ, D'Agostino RB Sr, Steyerberg EW. Extensions of net reclassification improvement calculations to measure usefulness of new biomarkers. *Stat Med*. 2011;30(1):11-21.
24. LoMauro A, Aliverti A. Sex differences in respiratory function. *Breathe (Sheffield, England)*. 2018;14(2):131-140.
25. Lee JG, Kim HC, Choi CM. Recent trends of lung cancer in Korea. *Tuberc Respir Dis*. 2021;84(2):89-95.
26. Tammemägi MC, Katki HA, Hocking WG, et al. Selection criteria for lung-cancer screening. *N Engl J Med*. 2013;368(8):728-736.
27. Chien JW, Au DH, Barnett MJ, Goodman GE. Spirometry, rapid FEV1 decline, and lung cancer among asbestos exposed heavy smokers. *COPD*. 2007;4(4):339-346.
28. 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.
29. Ballaz S, Mulshine JL. The potential contributions of chronic inflammation to lung carcinogenesis. *Clin Lung Cancer*. 2003;5(1):46-62.
30. Barnes PJ, Shapiro SD, Pauwels RA. Chronic obstructive pulmonary disease: molecular and cellular mechanisms. *Eur Respir J*. 2003;22(4):672-688.
31. Kc R, Shukla SD, Gautam SS, Hansbro PM, O'Toole RF. The role of environmental exposure to non-cigarette smoke in lung disease. *Clin Transl Med*. 2018;7(1):39.
32. Engels EA, Wu X, Gu J, Dong Q, Liu J, Spitz MR. Systematic evaluation of genetic variants in the inflammation pathway and risk of lung cancer. *Cancer Res*. 2007;67(13):6520-6527.
33. Stathopoulos GT, Sherrill TP, Cheng DS, et al. Epithelial NF-kappaB activation promotes urethane-induced lung carcinogenesis. *Proc Natl Acad Sci U S A*. 2007;104(47):18514-18519.
34. Hart K, Haugen A, Zienolddiny S. Allele-specific induction of IL1B -31T/C promoter polymorphism by lung carcinogens. *Mutation Res*. 2008;656(1-2):14-18.
35. Azad N, Rojanasakul Y, Vallyathan V. Inflammation and lung cancer: roles of reactive oxygen/nitrogen species. *J Toxicol Environ Health B Crit Rev*. 2008;11(1):1-15.
36. De la Garza MM, Cumpian AM, Daliri S, et al. COPD-type lung inflammation promotes K-ras mutant lung cancer through epithelial HIF-1α mediated tumor angiogenesis and proliferation. *Oncotarget*. 2018;9(68):32972-32983.
37. Young RP, Hopkins R, Eaton TE. Forced expiratory volume in one second: not just a lung function test but a marker of premature death from all causes. *Eur Respir J*. 2007;30(4):616-622.
38. Vestbo J, Edwards LD, Scanlon PD, et al. Changes in forced expiratory volume in 1 second over time in COPD. *N Engl J Med*. 2011;365(13):1184-1192.
39. Mannino DM, Reichert MM, Davis KJ. Lung function decline and outcomes in an

adult population. *Am J Respir Crit Care Med*. 2006;173(9):985-990.

40. Celli BR, Anderson JA, Cowans NJ, et al. Pharmacotherapy and lung function decline in patients with chronic obstructive pulmonary disease. A systematic review. *Am J Respir Crit Care Med*. 2021;203(6):689-698.
41. Lange P, Celli B, Agustí A, et al. Lung-function trajectories leading to chronic obstructive pulmonary disease. *N Engl J Med*. 2015;373(2):111-122.
42. Han MK, Agusti A, Celli BR, et al. From GOLD 0 to pre-COPD. *Am J Respir Crit Care Med*. 2021;203(4):414-423.
43. Papi A, Casoni G, Caramori G, 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.
44. Cancer Genome Atlas Research Network. Comprehensive genomic characterization of squamous cell lung cancers. *Nature*. 2012;489(7417):519-525.
45. Rhee CK. High prevalence of chronic obstructive pulmonary disease in Korea. *Korean J Intern Med*. 2016;31(4):651-652.

FLA 5.6.0 DTD ■ CHEST4978_proof ■ 26 April 2022 ■ 1:39 pm ■ EO: CHEST-21-3489