CHEST Online Supplement

Features of COPD as Predictors of Lung Cancer

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e-Appendix 1.

Methods

The study population was recruited from among participants in the COPDGene Study *(http://www.copdgene.org/)*, an ongoing National Heart Lung and Blood Institute–funded multicenter observational study involving 21 centers in the United States (clinical trial registration no. NCT00608764)[E1]. The Institutional Review Board (IRB) of each participating center approved the COPDGene Study, and all subjects provided written informed consent. Ann Arbor VA IRB (2014-060462), IRB for Baylor College of Medicine (H-22209), Partners Human Research Committee (2007-P000554), Columbia University IRB (AAAC9324), Duke University Health System IRB (Pro00004464), Johns Hopkins Medicine IRB (NA-00011524), IRB for Human Subjects Research for Baylor College of Medicine (H-22202) John F. Wolf, M.D. Human Subjects Committee (12756-03) Minneapolis VA Health Care System (4128-A) Health Partners IRB (07-127), Morehouse School of Medicine IRB (97826), National Jewish Health IRB (HS-1883a) Reliant Medical Group IRB (1441), Temple IRB (21659), University of Alabama at Birmingham for Human Use (F070712014), University of California, San Diego Human Research Protections Program (140070), University of Iowa IRB (2007 0712014), University of Michigan Medical School IRB (HUM00014973), University of Minnesota IRB (0801M24949), University of Pittsburgh IRB (#07120059) and UT Health Science Center San Antonio IRB (HSC 2007 0644H). The National Jewish Health IRB (HS-1825), Partners HealthCare Research Committee (2007P-000554), Temple IRB (20160339), and University of Pittsburgh IRB (PRO15100455) approved additional medical record review and the data analysis.

Subjects aged 45–80 years with $\geq$ 10 pack-year history of smoking underwent spirometry and high-resolution chest CT, measurements of height and weight, respiratory and quality of life questionnaires.[E1] A respiratory medication history questionnaire was also administered at the time of study entry. Subjects were asked yes/no questions regarding current medication use, as grouped by medication class. Classes included tiotropium bromide, inhaled corticosteroids (ICS), combination ICS and long-acting beta-agonists, short-acting beta-agonists, and short-acting anti-muscarinic agents. In a subgroup of subjects, blood was collected for biomarker analysis, as previously published.[E2] Spirometry was performed by using the EasyOne spirometry system (NDD, Zurich, Switzerland) before and after the administration of albuterol[E1]. Post- bronchodilator spirometry was used to determine severity of obstruction.

Imaging: Whole-lung volumetric multidetector CT was performed at full inspiration by using a standardized protocol [E1], and the lower-spatial-resolution smooth reconstruction algorithm was used for quantitative analysis. Quantitative analysis of emphysema severity was performed on segmented lung images by using the Slicer software package *(http://www.slicer.org/)*. The total emphysema percentage was defined as all lung voxels with a CT attenuation value of less than −950 HU. Automated airway analysis was performed by using the VIDA Pulmonary Workstation, version 2.0 (Vida Diagnostics, Coralville, Iowa, *http://www.vidadiagnostics.com/*) [E3]. Morphologic measurements were obtained along the center line of the lumen, in the middle third of the airway segment. Airway wall thickness was used as the quantitative CT measures of airway wall thickness [E4,E5]. Visual analysis for centrilobular and paraseptal emphysema was performed by two trained readers, with discordant reading adjudicated by a thoracic radiologist[E6]. Parenchymal emphysema was scored on a scale of 0 to 5: none, trace, mild, moderate, confluent and advance-destructive[E7]. Paraseptal emphysema was scored into three categories: none, mild and substantial. The CT images used in this study were anonymized in compliance with the Health Insurance Portability and Accountability Act.

Developement of Cohort: Lung cancer cases were identified through longitudinal follow-up and collection of death certificates. During follow-up, if a subject self-reported a new diagnosis of lung cancer this was verified by review of medical records. In addition, the COPDGene Data Coordinating Center, (DCC) obtained vital statistics data retrieved from the National Death Index by subject Social Security Number. If the death certificate listed lung cancer as a cause of death, the subject was included as a case. Additional lung cancer annotation was performed for those cases in which pertinent medical records were available. Deidentified data were reviewed and verified for accuracy by a medical oncologist. At the data cutoff of 12-31-2016, 169 lung cancer cases were verified with 116 annotated for date of diagnosis, histology, and stage, per available records (Figure E1a, Supplementary material).

References

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e-Table 1. Characteristics of Lung Cancer Cases and Controls, Subjects with $FEV_1/FVC < 0.7$			
Variable	**Cases (n = 126)**	**Controls (n = 504)**	**p Value**
Clinical Characteristics			
Age at Enrollment (Average)	67.1 (6.6)	65.7 (7.0)	
Race (NHW/AA)	81%/19%	77.8%/22.2%	
Gender (Male/Female)	54%/46%	52.4%/47.6%	
Smoking Status (Current/Former/Never)	64.3%/35.7%/0	62.7%/37.3%/0	
Average Pack years	59.4 (32.1)	56.6 (31.9)	
Years Since Quitting	6.9 (8.8)	7.5 (9.1)	
Exacerbation Frequency (per 12 months)	0.7 (1.2)	0.5 (1.0)	0.02
Body Mass Index	27.9 (6.4)	27.8 (5.5)	0.91
Spirometry			
FEV_1 ppd	48.6 (19.9)	59.9 (21.1)	<.0001
FEV_1/FVC	0.5 (0.1)	0.6 (0.1)	< .0001
GOLD Stage 1	5.6% (7)	18.8% (95)	< .0001
Stage 2	42.1% (53)	45.2% (228)	0.58
Stage 3	33.3% (42)	28.2% (142)	0.30
Stage 4	19% (24)	7.7% (39)	< .0001
Quantitative CT Measurements			
Emphysema (LAA -950)	15.4% (12.2%)	11.8% (11.7%)	.007
Emphysema: Upper /Lower Lobe Ratio	1.9 (2.2)	2.2 (2.8)	.16
Expiratory Gas Trapping (LAA -856)	44.5% (17.8%)	36.1% (19.5%)	<.0001
Pi10	3.7 (0.1)	3.7 (0.1)	.002
Visual Emphysema: Centrilobular			
None/trace	4.8% (6)	25.4% (128)	<.0001
Mild	15.1% (19)	22.2% (112)	0.1
Moderate	38.1% (48)	24.4% (123)	0.002
Confluent	26.2% (33)	18.5% (93)	0.06
Advanced/Destructive	11.1% (14)	9.5% (48)	0.71
No Visual Assessment	4.7% (6)	0 (0)	
Visual Emphysema: Paraseptal			
None	47.6% (60)	45.4% (229)	0.73
Mild	15.9% (20)	25.4% (128)	0.03
Substantial	31.7% (40)	29.2% (147)	0.64
No Visual Assessment	4.7% (6)	0 (0)	

NHW: Non-Hispanic White, AA: African-American, FEV_1: forced expiratory volume in 1 second, ppd: percentage predicted, FVC: forced vital capacity, GOLD: Global initiative for Chronic Lung Disease, HU: Hounsfield units, Pi10: 10mm internal perimeter

e-Table 2. Univariate Associations with the Diagnosis of Lung Cancer Subjects with FEV1/FVC <0.7		
Variable	**Odds Ratio (Standard deviation)**	**p Value**
Clinical Characteristics		
Exacerbation frequency 12 months prior to enrollment – (0-6)	1.04 (1.01-1.07)	0.009
Inhaled corticosteroid use	1.24 (1.13-1.37)	<0.001
Inhaled corticosteroid with LABA	1.02 (0.95-1.09)	0.47
Any inhaled corticosteroid	1.09 (1.03-1.17)	0.002
Tiotropium use	1.14 (1.06-1.21)	<0.001
Body mass index	1.0 (0.97-1.02)	0.09
Spirometry		
FEV_1 ppd per 10% decrease	1.04 (1.03-1.05)	<0.001
FEV_1/FVC per 10% decrease	1.07 (1.05-1.08)	<0.001
Bronchodilator response	0.99 (0.93-1.06)	0.97
Quantitative CT Measurements		
Emphysema (percent HU -950) per 10% increase	1.03 (1.01-1.06)	0.005
Emphysema: Upper Lobe/Lower Lobe Ratio Per 10%	0.93 (0.83-1.04)	0.23
Gas Trapping (percent HU –856) per 10% increase	1.03 (1.01-1.05)	<0.001
Pi10	1.42 (1.12-1.79)	0.003
Visual Emphysema		
Centrilobular: none-trace vs mild-advanced	1.21(1.12-1.29)	<0.001
Paraseptal: none vs mild	0.91 (0.85-0.98)	0.02
Paraseptal: none vs substantial	1.01 (0.95-0.19)	0.57

LABA: long-acting beta-agonist, FEV_1: forced expiratory volume in one second, ppd: percentage predicted, FVC: forced vital capacity HU: Hounsfield units, Pi10: 10mm internal perimeter. Cases and controls were matched for age, race, gender, smoking status, smoking pack-years, and years since quitting.

e-Table 3. Associations with the Diagnosis of Lung Cancer With covariates: Age, Gender, Race, Smoking Status, Pack-years, Years since quitting, FEV1/FVC		
Variable	**Odds Ratio (Standard deviation)**	**p Value**
Clinical Characteristics		
Exacerbation frequency 12 months prior to enrollment – (0-6)	1.47 (1.12--1.93)	0.004
Inhaled corticosteroid with LABA	0.93 (0.60-1.43)	0.76
Any inhaled corticosteroid	1.44 (0.93-2.23)	0.09
Tiotropium use	1.28 (0.82-1.99)	0.26
Body mass index	0.88 (0.64-1.20)	0.45
Spirometry		
FEV_1 ppd per 5% decrease	1.14 (1.10-1.18)	<0.001
Quantitative CT Measurements		
Emphysema (percent HU -950) per 10% increase	1.33 (0.76-2.33)	0.31
Emphysema (percent HU -950) > 5%	1.05 (0.93-1.20)	0.39
Emphysema: Perc15	1.05 (0.95-1.16)	0.27
Emphysema: log (percent HU -950)	1.04 (0.75-1.43)	0.81
Emphysema: Upper Lobe/Lower Lobe Ratio Per 5%	0.97 (0.63--1.32)	0.36
Gas Trapping (percent HU –856) per 5% increase	1.01 (0.91-1.09)	0.99
Pi10	2.12 (0.47-9.31)	0.31
Visual Emphysema		
Centrilobular: none-trace vs mild-advanced	2.33 (1.49-3.94)	0.001

Multivariable logistic regression with covariates: Age, Gender, Race, Smoking Status, Pack-years, Years since quitting, FEV1/FVC. LABA: long-acting beta-agonist, FEV_1: forced expiratory volume in one second, ppd: percent predicted, HU: Hounsfield units, Perc15: 15^{th} percentile of lung density, Pi10: 10mm internal perimeter.

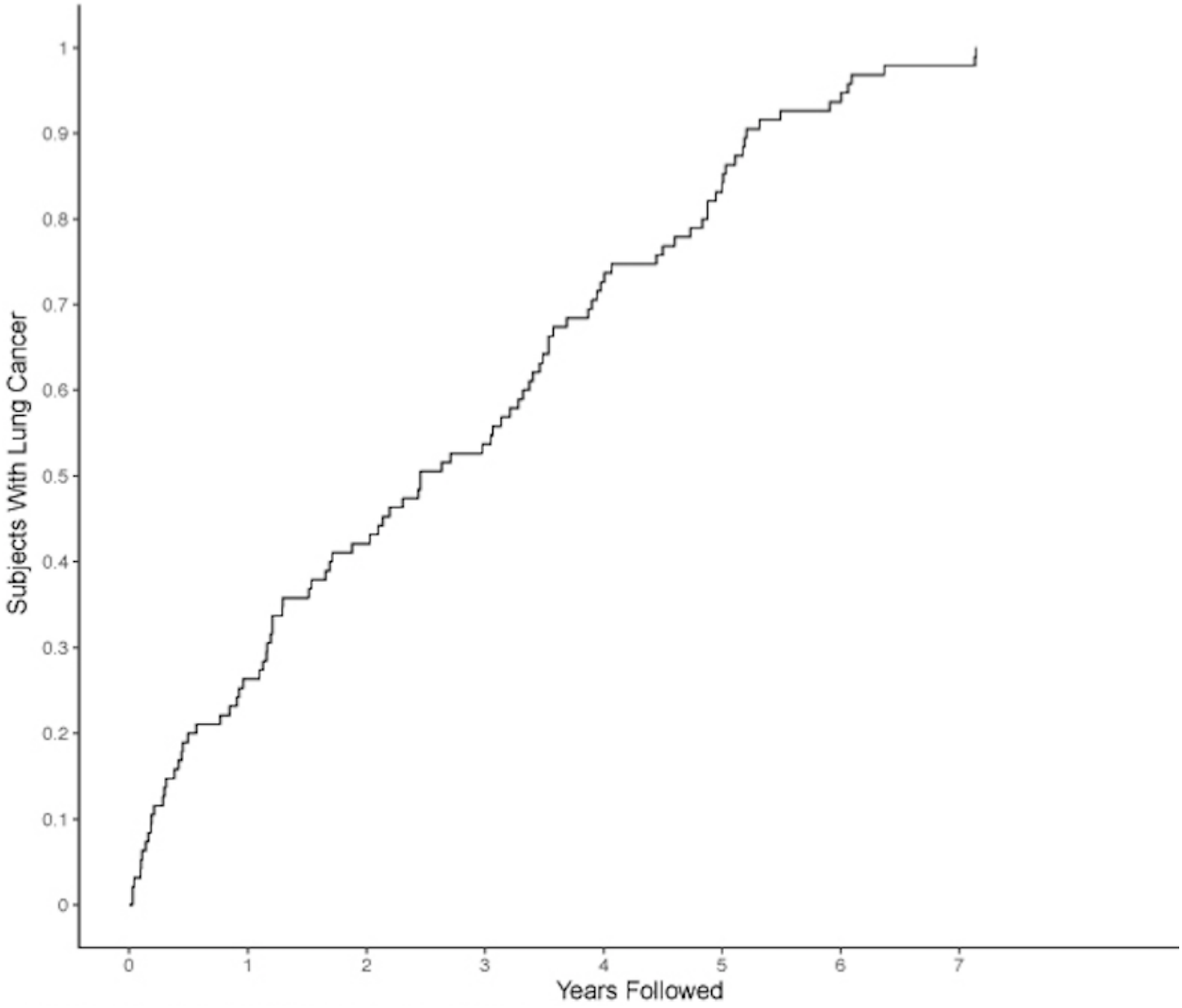
e-Table 4. Factors Associated with a Lung Cancer Diagnosis in the Multivariable Model Subjects with FEV1/FVC < 0.7		
	Lung Cancer Diagnosis	
Factor	Odds Ratio (95% CI)	p value
FEV_1 ppd – per 5% decrease	1.11 (1.05-1.17)	<0.001
Exacerbations in year prior to enrollment per event increase – 0, 1, ≥ 2	1.20 (0.89-1.61)	0.21
Visual Emphysema None-trace vs mild-advanced	5.02 (2.30-13.21)	<0.001

CI: confidence interval, FEV_1ppd: forced expiratory volume in one second percentage predicted, FVC: forced vital capacity. Cases and controls were matched for age, race, gender, smoking status, smoking pack-years, and years since quitting.

e-Table 5. Factors Associated with Histologic Type in the Multivariable Model Subjects with FEV1/FVC < 0.7		
	NSCLC as reference compared with SCLC (n=116)	
Factor	Odds Ratio (95% CI)	p value
FEV_1ppd – per 5% decrease	1.03 (0.87-1.20)	0.75
Exacerbations in year prior to enrollment per event increase 0, 1, ≥ 2	4.0 (1.58-10.75)	0.004
Visual Emphysema None-trace vs mild-advanced	0.18 (0.03-0.90)	0.04
Gender - male as reference	0.19 (0.03-0.75)	0.02

NSCLC: non-small cell lung cancer, SCLC: small cell lung cancer, CI: confidence interval, FEV_1ppd: forced expiratory volume in one second, percentage predicted, FVC: forced vital capacity.

e-Figure 1. Time interval between COPDGene study enrollment date and data of diagnosis. Analysis limited to cases with annotation to determine date of lung cancer diagnosis (n = 116).



e-Figure 2. Flow chart of lung cancer case identification.