Associations between emphysema-like lung on CT and incident airflow limitation: a general population-based cohort study

ABSTRACT

Emphysema on CT is associated with accelerated lung function decline in heavy smokers and patients with COPD; however, in the general population, it is not known whether greater emphysema-like lung on CT is associated with incident COPD. We used data from 2045 adult participants without initial prebronchodilator airflow limitation, classified by $FEV_1/FVC<0.70$, in the Multi-Ethnic Study of Atherosclerosis. Emphysema-like lung on baseline cardiac CT, defined as per cent low attenuation areas$_{<-950HU}$>upper limit of normal, was associated with increased odds of incident airflow limitation at 5-year follow-up on both prebronchodilator (adjusted OR 2.62, 95% CI 1.47 to 4.67) and postbronchodilator (adjusted OR 4.38, 95% CI 1.63 to 11.74) spirometry, independent of smoking history. These results support investigation into whether emphysema-like lung could be informative for COPD risk stratification.

INTRODUCTION

COPD risk assessment is important to developing and targeting primary prevention and precision medicine approaches to COPD, the fourth leading cause of death. Emphysema, defined pathologically by destruction of alveolar walls, is frequently observed in COPD; nonetheless, emphysema may occur in the absence of the airflow limitation that defines COPD, and, in postmortem series, has been observed in up to one-tenth of never smokers.[1]

Emphysema-like lung on CT—which has been previously validated against pathological samples of emphysema,[2 3] but which may also correspond to hyperinflation—is associated cross-sectionally with COPD, and has been associated longitudinally with respiratory and all-cause mortality in both patients with COPD and in persons with normal lung function.[4–6] Among smokers with COPD, areas of normal-appearing lung have been found to be mechanistically influenced by areas of emphysema-like lung, and the extent of emphysema-adjacent 'at risk' lung was associated with lung function decline.[7] Nonetheless, whether otherwise healthy individuals with greater proportions of emphysema-like lung are at increased risk of developing incident COPD is unknown.

Using information from the US general population-based Multi-Ethnic Study of Atherosclerosis (MESA), we identified 2045 middle-aged and older adults without prebronchodilator (BD) airflow limitation ($FEV_1/FVC<0.70$) on initial spirometry in 2004–2006. In this group, we tested whether the percentage of emphysema-like lung (voxels <-950 HU (Hounsfield units), or 'percent emphysema') on cardiac CT at cohort baseline (2000–2002) was associated with incident airflow limitation on pre-BD and post-BD spirometry in 2010–2012. Methods for MESA, statistical analyses, and selection and characteristics of participants are described in detail in the online supplementary tables S1–S4 and figure S1.

RESULTS

Mean age was 58.4 years at baseline, 54.0% were female, and 75.5% were non-White. Half of participants were never smokers. Among smokers, 47.7% reported <10 pack-years, and 11.3% reported more than 30 pack-years.

Percent emphysema

Median per cent emphysema was 2.65% (IQR, 1.17, 4.99). For each participant, the upper limit of normal (ULN) for per cent emphysema was defined by previously published reference equations derived in MESA accounting for age, gender, race/ethnicity, height, weight, current smoking and scanner parameters.[8] The prevalence of per cent emphysema>ULN was 5.4%.

Airflow limitation

Eleven per cent (n=224) developed incident pre-BD airflow limitation. Affected participants were older, weighed less and had lower initial lung function compared with those unaffected; 12.1% had a prior diagnosis of asthma, and 43.8% were never smokers.

Associations between per cent emphysema and incident airflow limitation

In fully adjusted models, per cent emphysema>ULN was associated with increased odds of incident airflow limitation both pre-BD (OR 2.62, 95% CI 1.47 to 4.67) and post-BD (OR 4.38, 95% CI 1.63 to 11.74). Results were similar in unadjusted models and robust to adjustment for initial FEV_1/FVC ratio. Associations were consistent for the continuous measure of per cent emphysema (table 1) as well as for a fixed threshold (>5% per cent emphysema) (see online supplementary

table S5). There was no evidence of effect measure modification by age, sex or race/ethnicity (p>0.2).

Sensitivity analyses

Results were similar in never smokers and ever smokers, and multiplicative interaction terms with smoking status were not statistically significant (see online supplementary table S6). Among ever smokers with 30+ pack-years, per cent emphysema was associated with adjusted ORs of 2.98 (per SD, 95% CI 1.63 to 5.41) and 5.45 (per SD, 95% CI 1.59 to 18.69) for incident pre-BD and post-BD airflow limitation, respectively.

Associations were not substantially altered by adjustment for education, site, self-reported emphysema and asthma, second-hand smoke, exposure to fumes, coronary artery calcium score, initial FEV_1/FVC, or fine particulate matter, nor by exclusion of participants with baseline asthma or respiratory symptoms (see online supplementary figure S2).

These findings were robust to redefinition of pre-BD airflow limitation by lower limit of normal criteria; classification of incident COPD as post-BD airflow limitation with respiratory symptoms; and multiple imputation of missing post-BD spirometry (see online supplementary figure S2).

Additional results are provided in online supplement.

DISCUSSION

Greater per cent emphysema on CT was associated with incident pre-BD and post-BD airflow limitation at 5-year follow-up in a contemporary, multiethnic, population-based cohort of middle-aged and older adults. These results were independent of lung function and standard clinical risk factors, including smoking.

This is the first work, to our knowledge, to show that the extent of emphysema-like lung is associated with the development of airflow limitation in otherwise healthy adults, including in never smokers. Our results are consistent with mounting evidence that measures of emphysema on CT may be associated with clinical outcomes in the absence of spirometry-defined COPD. We previously demonstrated in this cohort that per cent emphysema was associated with all-cause mortality in persons without airflow limitation or COPD, mostly from respiratory mortality.[5 6] The current work indicates that the adverse prognosis of per cent emphysema on mortality may be attributable, in part, to an elevated risk of

Table 1 Emphysema-like lung on CT and incidence of airflow limitation at 5-year follow-up

Model*	Cases/at risk	Per cent emphysema>upper limit of normal (dichotomous)†		Per cent emphysema log transformed (continuous)	
		OR (95% CI)‡	p Value	OR per SD (95% CI)‡	p Value
Incident prebronchodilator airflow limitation§	224/2045				
Unadjusted		1.86 (1.12 to 3.09)	0.016	1.64 (1.39to 1.94)	<0.001
Minimally adjusted		2.07 (1.22 to 3.51)	0.007	1.48 (1.23 to 1.77)	<0.001
+age, sex, race/ethnicity					
Fully adjusted		2.62 (1.47 to 4.67)	0.001	1.92 (1.55 to 2.38)	<0.001
+height, weight, CT scanner, smoking history, initial FEV_1					
Extended		2.41 (1.32 to 4.40)	0.004	1.61 (1.28 to 2.03)	<0.001
+initial FEV_1/FVC					
Incident postbronchodilator airflow limitation§	53/1915				
Unadjusted		2.47 (1.03 to 5.94)	0.043	1.91 (1.35 to 2.69)	<0.001
Minimally adjusted		2.56 (1.05 to 6.25)	0.040	1.79 (1.23 to 2.60)	0.003
+age, sex, race/ethnicity					
Fully adjusted		4.38 (1.63 to 11.74)	0.003	2.59 (1.65 to 4.08)	<0.001
+height, weight, CT scanner, smoking history, initial FEV_1					
Extended		4.63 (1.71 to 12.53)	0.003	2.36 (1.47 to 3.79)	<0.001
+initial FEV_1/FVC					

*Logistic regression models were sequentially adjusted. The minimally adjusted model includes study baseline age, sex and race/ethnicity. The fully adjusted model additionally includes height, weight, CT type, smoking status, pack-years, urinary cotinine and FEV_1 per cent predicted at the initial spirometry exam. The extended model also includes initial FEV_1/FVC ratio.
†The ULN for per cent emphysema on cardiac CT was defined according to reference equations developed in the same cohort accounting for age, gender, race/ethnicity, height, weight, current smoking and scanner parameters.[8]
‡ORs reported for presence versus absence of per cent emphysema>ULN or per SD (3.1%) of log-transformed per cent emphysema, with 95% CI.
§Airflow limitation was defined as FEV_1/FVC<0.700.[10]
ULN, upper limit of normal.

developing airflow limitation.

Although we used a definition of per cent emphysema that has been validated against tissue specimens of emphysema in multiple studies,[2 3 9] the pathological significance of greater emphysema-like lung in healthy never smokers is not completely known. Hyperinflation and gas trapping could contribute to lower lung density on CT; however, exclusion of participants with asthma did not alter our results. Whatever the pathophysiological basis, our findings suggest that per cent emphysema>ULN may be associated with increased risk of developing airflow limitation meeting spirometric criteria for COPD.[10]

Per cent emphysema was calculated from low-dose cardiac CT scans, which imaged only the lower two-thirds of the lungs, yet these measures have been shown to correlate closely with measures from full-lung scans.[11] Older CT technology relied upon in this study may also have introduced random measurement error; hence, measuring per cent emphysema on the contemporary full-lung CTs that are currently indicated for lung cancer screening in heavy smokers—among whom we demonstrated a strong association—would be expected to yield more precise results.

Follow-up was limited to two spirometry exams and there was a relatively low incidence of airflow limitation over 5-year follow-up. Post-BD spirometry was also missing for a substantial number of participants with incident airflow limitation. Nonetheless, our results were consistent in both adjusted and unadjusted models, and similar in sensitivity analyses using multiple imputation.

In conclusion, emphysema-like lung on CT was associated with incident airflow limitation in a general population-based cohort, independent of smoking and other major known risk factors for COPD. These results support investigation into whether per cent emphysema could be informative for COPD risk stratification.

Elizabeth C Oelsner,[1,2] Benjamin M Smith,[1,3] Eric A Hoffman,[4] Aaron R Folsom,[5] Steven M Kawut,[6] Joel D Kaufman,[7] Ani Manichaikul,[8] David J Lederer,[1] Joseph E Schwartz,[1] Karol E Watson,[9] Paul L Enright,[10] John H M Austin,[1] Joao A C Lima,[11] Steven J Shea,[1,2]

Robert G Barr[1,2]

[1]Department of Medicine, Columbia University College of Physicians and Surgeons, New York City, New York, USA
[2]Department of Epidemiology, Columbia University Mailman School of Public Health, New York City, New York, USA
[3]Respiratory Division, McGill University, Montreal, Quebec, Canada
[4]Department of Radiology, University of Iowa, Iowa City, Iowa, USA
[5]Division of Epidemiology and Community Health, University of Minnesota, Minneapolis, Minnesota, USA
[6]School of Medicine, Pulmonary, Allergy and Critical Care Division, University of Pennsylvania, Philadelphia, Pennsylvania, USA
[7]Department of Environmental and Occupational Health Sciences, University of Washington, Seattle, Washington, USA
[8]Department of Public Health Sciences, Division of Biostatistics and Epidemiology, University of Virginia, Charlottesville, Virginia, USA
[9]Division of Cardiology, UCLA School of Medicine, Los Angeles, California, USA
[10]Department of Medicine, University of Arizona, Tucson, Arizona, USA
[11]Department of Cardiology, Johns Hopkins University, Baltimore, Maryland, USA

Correspondence to Dr Elizabeth C Oelsner, Department of Medicine, Columbia University Medical Center, Presbyterian Hospital, New York, NY 10032, USA; eco7@cumc.columbia.edu

of participating MESA investigators and institutions can be found at http://www.mesa-nhlbi.org.

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/thoraxjnl-2017-210842).

Check for updates

REFERENCES

1 Auerbach O, Hammond EC, Garfinkel L, *et al*. Relation of smoking and age to emphysema. whole-lung section study. *N Engl J Med* 1972;286:853–7.
2 Gevenois PA, de Maertelaer V, De Vuyst P, *et al*. Comparison of computed density and macroscopic morphometry in pulmonary emphysema. *Am J Respir Crit Care Med* 1995;152:653–7.
3 Gevenois PA, De Vuyst P, de Maertelaer V, *et al*. Comparison of computed density and microscopic morphometry in pulmonary emphysema. *Am J Respir Crit Care Med* 1996;154:187–92.
4 Johannessen A, Skorge TD, Bottai M, *et al*. Mortality by level of emphysema and airway wall thickness. *Am J Respir Crit Care Med* 2013;187:602–8.
5 Oelsner EC, Hoffman EA, Folsom AR, *et al*. Association between emphysema-like lung on cardiac computed tomography and mortality in persons without airflow obstruction: a cohort study. *Ann Intern Med* 2014;161:863–73.
6 Oelsner EC, Carr JJ, Enright PL, *et al*. Per cent emphysema is associated with respiratory and lung cancer mortality in the general population: a cohort study. *Thorax* 2016;71:624–32.
7 Bhatt SP, Bodduluri S, Hoffman EA, *et al*. Computed tomography measure of lung at risk and lung function decline in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2017;196:569–76.
8 Hoffman EA, Ahmed FS, Baumhauer H, *et al*. Variation in the percent of emphysema-like lung in a healthy, nonsmoking multiethnic sample. The MESA lung study. *Ann Am Thorac Soc* 2014;11:898–907.
9 Madani A, Keyzer C, Gevenois PA. Quantitative computed tomography assessment of lung structure and function in pulmonary emphysema. *Eur Respir J* 2001;18:720–30.
10 Vogelmeier CF, Criner GJ, Martinez FJ, *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;195:557–82.
11 Hoffman EA, Jiang R, Baumhauer H, *et al*. Reproducibility and validity of lung density measures from cardiac CT Scans-The Multi-Ethnic Study of Atherosclerosis (MESA) lung study. *Acad Radiol* 2009;16:689–99.