Online Data Supplement

Reduced Expiratory Flow Rate among Heavy Smokers Increases Lung Cancer Risk: Results from the NLST-ACRIN Cohort (N=18, 714)

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eTable 1. Lung cancer prevalence according to Airflow limitation or GOLD status and screening arm (CT vs CXR) in the NLST-ACRIN cohort (N=18,475).

COPD status	**CT arm**		**CXR arm**		**Total**	
	LC/Total	Lung Cancer Prevalence	LC/Total	Lung Cancer Prevalence	LC/Total	Lung Cancer Prevalence
GOLD 1	44/796	5.53%	34/811	4.19%	78/1607	4.85%
GOLD 2	99/1731	5.72%	114/1797	6.34%	213/3528	6.04%
GOLD 3	43/541	7.95%	45/542	8.30%	88/1083	8.13%
GOLD 4	13/110	11.82%	8/101	7.92%	21/211	9.95%
Airflow Limitation	200/3183	6.28%	201/3253	6.18%	401/6436	6.23%
No Airflow limitation	193/6047	3.19%	164/5990	2.74%	357/12037	2.97%
Total	393/9230	4.26%	365/9243	3.95%	758/18473	4.10%

eTable 2. Unadjusted and adjusted odd ratios from multiple logistic regression for lung cancer associations with CT-based emphysema (curvilinear relationship) and GOLD-based airflow limitation (linear relationship) from the PluSS (Table 3 in ref 7).

			Unadjusted		**Adjusted[1]**		**Adjusted[2]**	
	Cases	*Noncases*	*OR*	*95% CI*	*OR*	*95% CI*	*OR*	*95% CI*
Airflow Obstruction								
None	32	2053	Ref		Ref		Ref	
GOLD 1	16	477	2.15	1.17-3.95	1.66	0.89-3.11	1.13	0.59-2.17
GOLD 2	36	792	2.92	1.80-4.73	2.11	1.27-3.49	1.47	0.87-2.50
GOLD 3-4	15	217	4.43	2.36-8.32	2.86	1.48-5.53	1.87	0.92-3.80
Radiographic Emphysema								
None	24	2068	Ref		Ref			
Trace	22	663	2.86	1.59-5.13	2.58	1.43-4.66	2.48	1.37-4.49
Mild	37	493	6.47	3.83-10.9	5.04	2.94-8.62	4.43	2.53-7.79
Mod-Severe	16	315	4.38	2.30-8.33	3.20	1.65-6.23	2.56	1.26-5.20

1 = adjusted for age, gender and smoking, 2 = adjusted for age, gender and smoking in addition to CT-emphysema for airflow limitation and GOLD for CT-based emphysema.

eTable 3. Univariate and multivariate logistic regressions predicting lung cancer according to age, pack years and FEV_1% predicted in the NLST-ACRIN cohort (N=18,473).

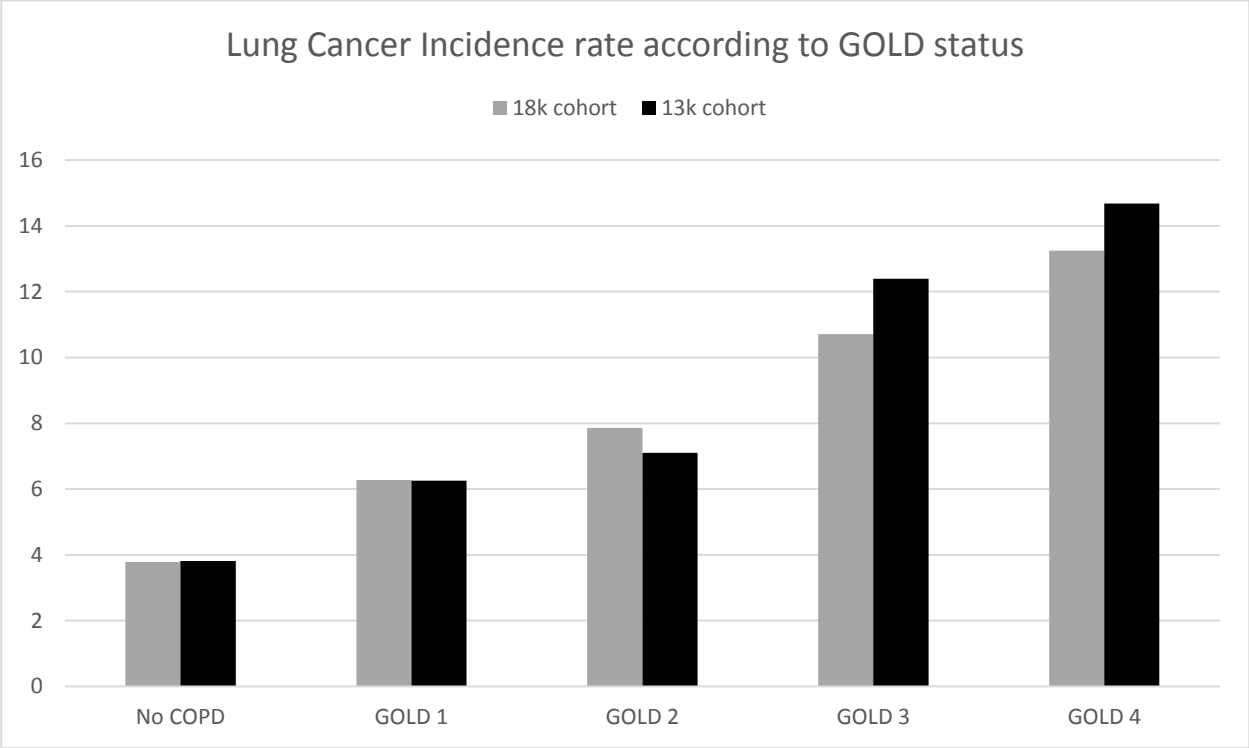
Model	**FEV_1%predicted[1]**		**Age[2]**		**Pack years[3]**	
Univariate	*Odds ratio*	*P value*	*Odds ratio*	*P value*	*Odds ratio*	*P value*
FEV1%predicted	2.29	<0.0001				
Age			2.13	<0.0001		
Pack Years					1.82	<0.0001
Multivariate						
FEV_1%pred and age	2.13	<0.0001	1.99	<0.0001		
FEV_1%pred and pack years	2.15	<0.0001			1.71	<0.0001
FEV_1%pred, age and pack years	2.02	<0.0001	1.90	<0.0001	1.62	<0.0001

[1]Odds ratio comparing FEV_1% predicted ≤60% vs. >60%.

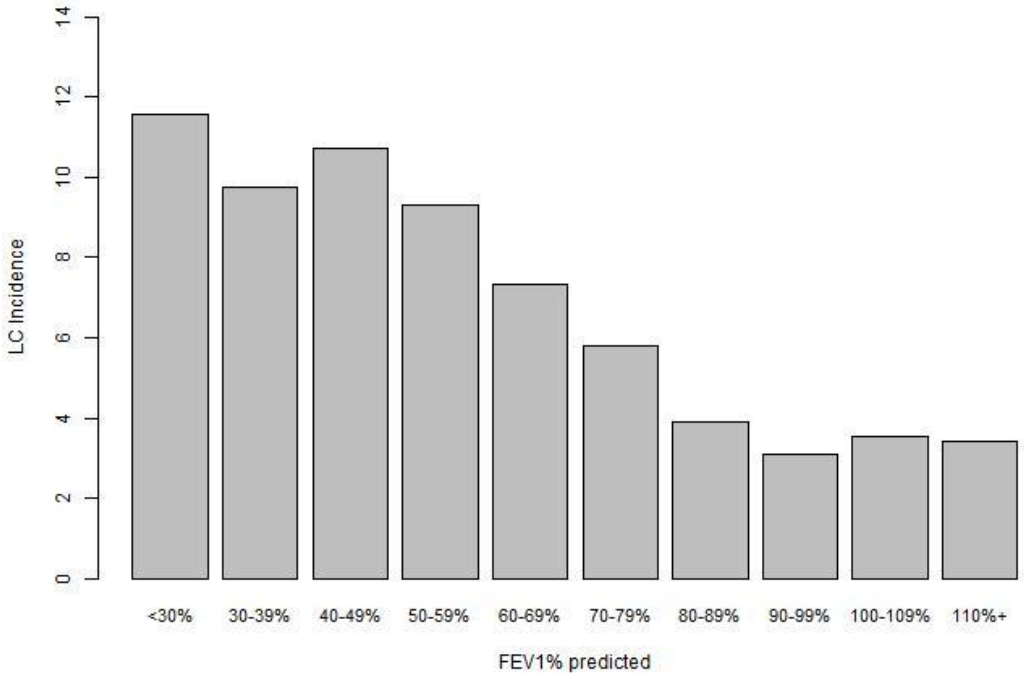
[2]Odds ratio comparing age > 59 years vs. ≤ 59 years.

[3]Odds ratio comparing pack years > 49 pack years vs. ≤ 49 pack years.

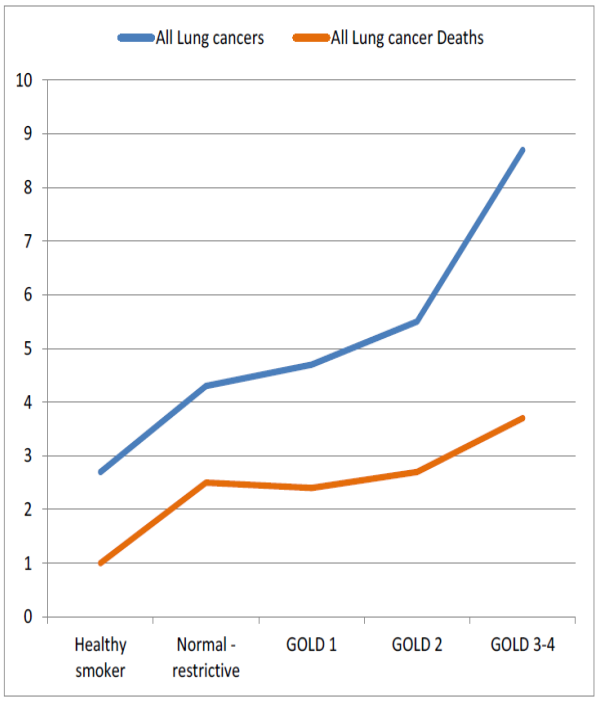
eFigure 1. Lung cancer incidence rate (per 1000 person years) in the NLST-ACRIN sub-cohort according to pre-bronchodilator spirometry-defined GOLD grade (GOLD 1-4) in the full cohort (18K cohort, grey) and those who meet strict ATS recommendations (13k cohort, black).

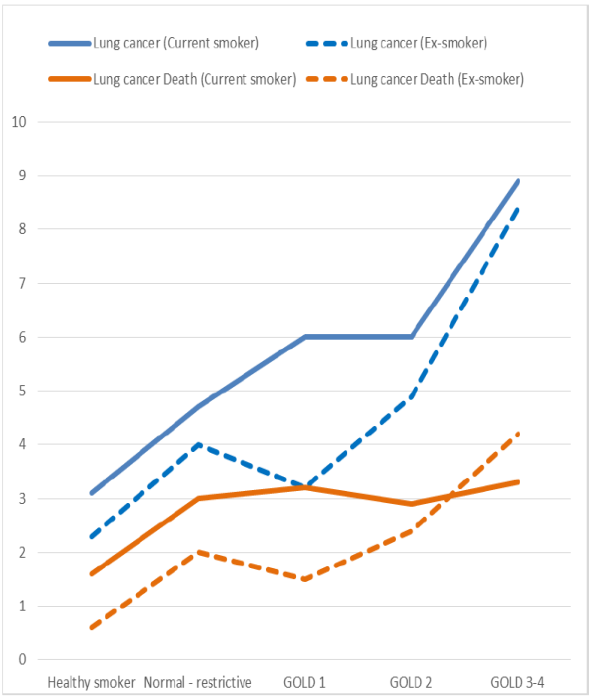


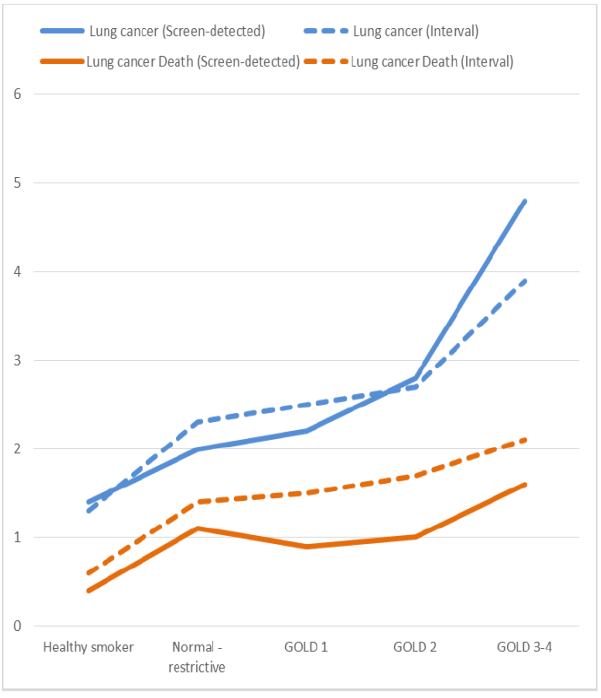
eFigure 2. Lung cancer incidence (per 1000 person years) according to FEV_1%predicted in the NLST-ACRIN substudy (N=18,473).

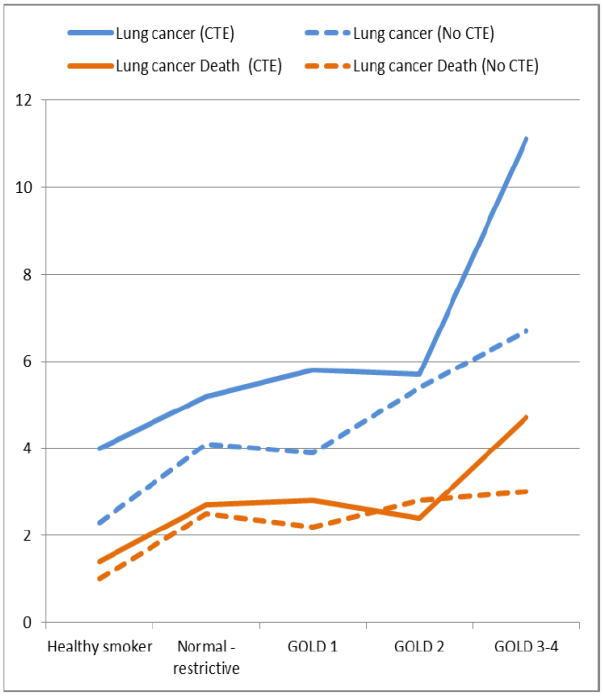


eFigure 3. Lung cancer prevalence (Blue) and mortality (Orange) as a percentage stratified by smoking status (Current vs Ex-smoker), lung cancer detection (Screen- detected vs Interval) and baseline emphysema (present (E+) vs absent (E-)).









Supplementary Discussion

Airflow limitation versus CT-quantified emphysema in lung cancer risk

There remains debate about the respective utility of using airflow limitation or CT-quantified emphysema in assessing the risk of lung cancer (6,7, R1-R7). Several studies have concluded that the risk of lung cancer was more robust using semi-quantitative assessment of emphysema (visual grading) than with automated emphysema scoring methods(R5,R6).

One study found that severe airflow limitation was associated with increased lung cancer risk but not CT-quantified emphysema(R1) although others have found the contrary (6,7). In the Pittsburgh Lung Cancer Screening Study (PluSS)(7), the investigators concluded that emphysema, based on semi-quantitative scoring (None, Trace, Mild and Moderate-severe) was more strongly correlated with risk of lung cancer than airflow limitation (eTable 2). However for CT-based emphysema, there is a curvilinear relationship with risk of lung cancer that weakened (but remained significant) after adjustment for airflow limitation based on GOLD(7). In contrast for airflow limitation based on GOLD, the linear relationship with risk of lung cancer was weakened and lost significance after correction for emphysema severity(7). These findings together with the observation that the presence of CT-based emphysema in the absence of airflow limitation is associated with lung cancer, lead these investigators to conclude that emphysema is the more relevant “COPD-related” phenotype linked to increased risk of lung cancer.

However, while this may be true, the results of the current study show that airflow limitation has a simple linear relationship with risk of lung cancer that remains clinically

useful in the setting of lung cancer risk assessment. This is the case whether the severity of airflow limitation is graded according to GOLD criteria (Figure 1 and 2) or assessed according to FEV_1%predicted (eFigure 2). This means that airflow limitation (or FEV_1%predicted) can be included in lung cancer risk models as a continuous variable, across the spectrum of severity, unlike CT-quantified emphysema which cannot because of its curvilinear relationship with lung cancer (eTable 2). The utility of using airflow limitation as a risk variable also stems from the clinical perspective that it is much simpler and cheaper to perform spirometry than a CT scan.

The most interesting result from the PLuSS was that the smokers with CT-based emphysema alone, GOLD 1-2 airflow limitation or GOLD 3-4 airflow limitation were 3 fold, 4 fold and 6 fold respectively, more likely to develop lung cancer than those with "Normal lungs". This suggests that airflow limitation and emphysema severity can be combined in order to best identify smokers at greatest and lowest risk of lung cancer. In this respect, we have shown that 85% of all lung cancers in the PLuSS study had one or other of these "COPD phenotypes"(9).

We estimate 4-fold more people with "normal lungs" will need to be screened to achieve comparable lung cancer diagnostic rates to those with mild-moderate (GOLD 1-2) COPD. The curvilinear relationship between CT-based emphysema and risk of lung cancer, where mild emphysema confers greater risk than trace or moderate-severe emphysema(7), may explain why studies do not consistently report an association between CT-based emphysema and risk of lung cancer(R1-R7). This inconsistency may also reflect the

differences in scoring emphysema severity using semi-quantitative methods compared to automated scoring systems(R6).

The nonlinear relationship between CT-based emphysema and risk of lung cancer might also underlie why the study of de Torres (10) found greater lung cancer incidence in those with mild airflow limitation (GOLD 1-2), where we hypothesise that the symptomatic clinic patients have a greater prevalence of mild emphysema than the asymptomatic screening participants. If such a hypothesis were true, then a combined approach to assessing risk of lung cancer might be used where a reduced DLCO(10) may be used instead of a CT scan to assess for the presence and severity of emphysema. Such an approach would also identify those with smoking-related restrictive lung disease also associated with an increased risk of lung cancer (Table 4)(4). As previously stated, the presence of emphysema was only reported as yes or no in this study (ie dichotomised), while other COPD-related phenotypes such as airway thickness, airway diameter, gas trapping or interstitial changes were not routinely collected and thus not available for analysis in this cohort. That said, the impact of airflow limitation on outcomes in CT screening in addition to lung cancer incidence is the subject of further analyses.

Lung Cancer Incidence and Histology – the effect of airflow limitation and "histology shift"

Another finding of this study was the significant differences in lung cancer incidence and lung cancer histology according to the presence and severity of airflow limitation (Tables 2 and 3). We estimate that the annual lung cancer incidence, regardless of screening interval, was

two-fold greater in participants with airflow limitation (GOLD 1-4) compared to those with normal lung function (Table 2).

A further finding in our study is the difference in histology according to the presence of airflow limitation. In those with airflow limitation at baseline, there were significantly fewer bronchioloalveolar cell cancers (Tables 2 and 3). There was also a trend towards fewer adenocarcinomas and more squamous cell carcinomas consistent with other studies. These differences in lung cancer histology, according to the presence of airflow limitation, were also evident with increasing severity of airflow limitation according to GOLD grade (Table 3).

For subjects with more severe airflow limitation (GOLD grade 3-4), we found less BAC and adenocarcinomas, and more squamous cell and Non-small cell lung cancers. This may explain the observation that COPD status is associated with more aggressive lung cancers(35,36). We and others have shown similar results in studies where lung cancers with a shorter volume doubling time (faster growth rate) were more prevalent in those with impaired lung function consistent with COPD(36,37). Moreover in the current study, in those who developed lung cancer but had airflow limitation at baseline, there were no excess cancers between the CT and CXR arms, there was comparable histology and a significant stage shift in favour of early stage cancer over late stage cancer (22). In those lung cancers found in screening subjects with no airflow limitation at baseline, we found an excess of cancers attributed entirely to early stage cancers of BAC histology. The importance of our observation that airflow limitation is associated with more aggressive lung cancer in the context of CT screening may have a bearing on the attenuated lung cancer-specific mortality found in this group(41) and remains the subject of further investigation.

Supplementary References

R1. 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: 1093-1098.

R2. Maldonado F, Bartholmai BJ, Swensen SJ, Midthun DE, Decker PA, Jett JR. Are airflow obstruction and radiographic evidence of emphysema risk factors for lung cancer? A nested case-control study using quantitative emphysema analysis. *Chest* 2010; 138: 1295-1302.

R3. Strange C. COPD and lung cancer: Are they both airways diseases? *Chest* 2010; 138: 1289-1290.

R4. Gierada DS, Guniganti P, Newmans BJ, Dransfield MT, Kvale PA, Lynch DA, et al. Quantitative CT assessment of emphysema and airways in relation to lung cancer risk. *Radiology* 2011; 261: 950-959.

R5. Carrozzi L, Viegi G. Lung cancer and chronic obstructive pulmonary disease: the story goes on. *Radiology* 2011; 261: 688-691.

R6. Smith BM, Pinto L, Ezer N, Sverzellati N, Munro S, Schwartzman K. Emphysema detected on computed tomography and risk of lung cancer: A systematic review and meta-analysis. *Lung Cancer* 2012; 77: 58-63.

R7. Sanchez-Salcedo P, Wilson DO, de Torres JP, Weissfield JL, Berto J, Campo A, et al. Improving selection for lung cancer screening: the potential role of emphysema. *Am J Respir Crit Care Med* 2015; 191: 924-931.