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Airflow limitation and mortality during cancer screening in the National Lung Screening Trial: why quantifying airflow limitation matters.

Robert P Young, MD, PhD, DSc[1], Ralph C Ward, PhD[2], Raewyn J Scott BN, MPH, PhD[1], Greg D Gamble, MSc[1], Gerard A Silvestri, MD MS[2].

Supplementary Methods

Clinical variables and Demographic variables

Clinical variables included BMI and patient self-reported comorbidities (COPD, adult asthma, chronic bronchitis, emphysema, pneumonia, heart disease, hypertension, stroke, diabetes, and any cancer. Lung cancer variables included histology type (small cell, squamous cell, adenocarcinoma, (where former bronchioloalveolar carcinoma (BAC) were included), non-small cell lung cancer – not otherwise specified (NSCLC-NOS), large cell, and other), lung cancer stage (I through IV and occult carcinoma), screen detection year (T0 through T7), screen results associated with diagnosed lung cancer (detected, missed/interval, follow-up). Smoking variables included pack years, cigarettes per day, current smoking status, years since quitting, total smoking duration, and family history of lung cancer. Demographic variables included age, sex, race-ethnicity (minority race-ethnicity or white), and education level (high school or less, post high school training, some college, college graduate, post-graduate or professional, other/unknown).

Pulmonary Function Testing

In the NLST-ACRIN cohort, pre-bronchodilator spirometry was measured at baseline screening (T0) in the majority of participants meeting previously published criteria. The spirometry was measured by trained staff using a Spiropro spirometer (eResearchTechnology, GmbH, Germany).[1] The severity of airflow limitation was defined according to the Global Initiative on Chronic Obstructive Lung Disease (GOLD) criteria grades 1-4 (www.GOLDCOPD.org accessed March 2, 2020); where Forced Expiratory Volume in one second in litres (FEV_1) and Forced Vital

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Capacity in litres (FVC) are used. Among patients with $FEV_1/FVC < 0.70$, COPD severity levels were: GOLD 1: $FEV_1 \geq 80\%$ predicted; GOLD 2: $50\% \leq FEV_1 < 80\%$ predicted; GOLD 3-4: $FEV_1 < 50\%$ predicted.

Lung Cancer Death Statistics (Table 3)

The lung cancer (LC) death statistics included: 1) the relative risk reduction in LC deaths; 2) the absolute number of LC deaths averted per 1000 patients based on the absolute difference in LC death rates scaled to 1000 patients; 3) absolute LC deaths averted per 1000 patient-years of follow-up based on the absolute difference of LC deaths per total patient-years followed until LC diagnosis; 4) the odds ratio (OR) for LC death based on the 2x2 table for the specific comparison; 5) the number needed to screen to avert 1 LC death.

Competing Cause of Death Analyses (Supplementary Table 2)

In further supplementary analyses, we conducted competing risk proportional hazards analyses (Fine and Gray subdistributional models)[3] with lung cancer death the primary event of interest and non-lung cancer death the competing risk. The primary exposure was screening group (CT vs. CXR), with adjustment for COPD severity, age, sex, race-ethnicity, body mass index (BMI), years since quit smoking, pack years, current smoking status, and all comorbidities. We tested for an interaction between screening group and COPD severity, and estimated cumulative incidence from the final model by COPD risk group and exposure level.

Supplementary Results

Figure 2 provides a summary of screening outcomes by COPD group. When the relative reduction in lung cancer mortality were compared according to screening arm, stratified by GOLD grade (Table 3), there were relative benefits (% difference) favouring those randomised to the CT arm for the non-COPD group (30%, $P<0.05$) and GOLD grade 1 or 2 (24% and 27% respectively, $P>0.05$). The estimated number needed to screen (NNS) to avert one lung cancer death with CT was 2-fold greater for GOLD groups 1 and 2, relative to non-COPD controls (129, 120 and 219 respectively).

In Supplementary Figure 2, we show that in the competing risk model (Fine and Gray), the estimated cumulative incidence of lung cancer deaths favours CT over CXR in non-COPD and GOLD 1-2 groups; these differences approached statistical significance in the model. For those with GOLD 3-4, the graphical representation shows little difference between CT and CXR, suggesting CT is less effective at reducing lung cancer deaths in those with GOLD 3-4 compared with other COPD groups.

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Supplementary References

1. Goodman, L. A., and Kruskal, W. H. (1979). Measures of Association for Cross Classification. New York: Springer-Verlag.

2. Fine, J. P., and Gray, R. J. (1999). "A Proportional Hazards Model for the Subdistribution of a Competing Risk." Journal of the American Statistical Association 94:496–509.

Supplementary Table 1. A comparison of lung cancer characteristics between non-COPD controls and screening subjects with GOLD 3-4 airflow limitation.

	Non-COPD Controls	COPD GOLD 3-4	P value
N=13,552 (% total)	N=12,303 (66.6%)	N=1,249 (6.8%)	
Lung Cancer Outcomes†			
Lung cancer diagnosis N (% group)	380 (3.1%)	115 (9.2%)	<0.0001
Lung Cancer death N (% group)	173 (1.4%)	57 (4.6%)	<0.0001
Lung Cancer lethality	45.5%	49.6%	0.46
Mean patient years follow-up	6.2 (1.0)	5.9 (1.4)	<0.0001
LC Surgery (N=%yes)	211 (55.5%)	44 (38.3%)	0.003
Lung Cancer Histology N (%LC)			
Small Cell	52 (13.7%)	15 (13.0%)	0.86
Squamous Cell	72 (18.9%)	31 (27.0%)	0.064
Adenocarcinoma (incl BAC)‡	174 (45.8%)	37 (30.4%)	0.0035
Non-small Cell-NOS	52 (13.7%)	26 (22.6%)	0.021
Large cell	14 (3.7%)	1 (0.87%)	0.21
Other/unknown	16 (4.2%)	7 (6.1%)	0.45
Lung Cancer Stage N (% LC))			
Stage I-II	182 (47.9%)	55 (47.8%)	0.99
Stage III	76 (20.0%)	21 (18.3%)	0.79
Stage IV	103 (27.1%)	30 (26.1%)	0.83
Occult carcinoma/unknown	19 (5.0%)	9 (7.8%)	0.25
Screen Detection			
Cancer Year N (% LC))			
-T0 (1st yr Screening)	95 (25.0%)	21 (18.3%)	0.25
-T0-2 (Screening Interval)	228 (60.0%)	60 (52.2%)	
-T3-T7 (Follow-up Interval)	152(40.0%)	55 (47.8%)	
Cancer Detection N (% LC)			
-Screen Detected	187 (49.2%)	49 (42.6%)	0.31
-Missed/Interval	41 (10.8%)	11 (9.6%)	
-Follow-up	152 (40.0%)	55 (47.8%)	

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Supplementary Table 2. Competing risk model‡ (Hazard Ratio) analyses for lung cancer death after screening

Effect	Hazard Ratio‡ (95% CI)	P-value
CT vs CXR at GOLD=1 or 2$^{\Phi}$	0.73 (0.52, 1.02)	0.063
CT vs CXR at GOLD= 3 or 4	0.93 (0.55, 1.57)	0.79
CT vs CXR at non-COPD	0.76 (0.56, 1.03)	0.073
Race-ethnicity: Minority race vs. White	0.85 (0.54,1.33)	0.472
Age (per year)	1.06 (1.04,1.09)	**<.0001**
Sex (female vs male)	1.02 (0.82,1.27)	0.8779
BMI (per unit)	0.98 (0.96,1.00)	0.0815
Years since quit smoking (per year)	0.95 (0.91,0.99)	**0.0065**
Pack years (per pack year)	1.01 (1.01,1.01)	**<.0001**
Current smoker (Y vs N)	1.35 (0.99,1.85)	0.0579
COPD (self-reported)	1.55 (1.12,2.15)	**0.0078**
Chronic bronchitis	1.00 (0.73,1.38)	0.9981
Emphysema	1.36 (1.01,1.83)	**0.0459**
Pneumonia	1.11 (0.88,1.40)	0.3752
Heart Disease	1.26 (0.95,1.65)	0.1031
Hypertension	1.00 (0.80,1.25)	0.9896
Adult asthma	0.58 (0.36,0.94)	**0.0268**
Stroke	0.93 (0.55,1.57)	0.7787
Diabetes	1.59 (1.15,2.21)	**0.0054**
History of other non-lung cancers	0.80 (0.46,1.38)	0.4193

‡Fine and Gray model treating non-lung cancer death as a competing event**.** CI=Confidence Interval.P<0.05 in bold.

$^{\Phi}$Legend: We combined GOLD 1 and 2 because they had very similar rates of LC incidence and death in our initial analysis (Table 2) and very similar screening outcomes favouring CT, specifically; relative reduction in lung cancer death (24% and 27%), absolute lung cancer deaths averted per 1000 subjects screened (7.8/1000 and 8.3/1000) and odds of lung cancer death (0.75 and 0.72) respectively (Table 3).

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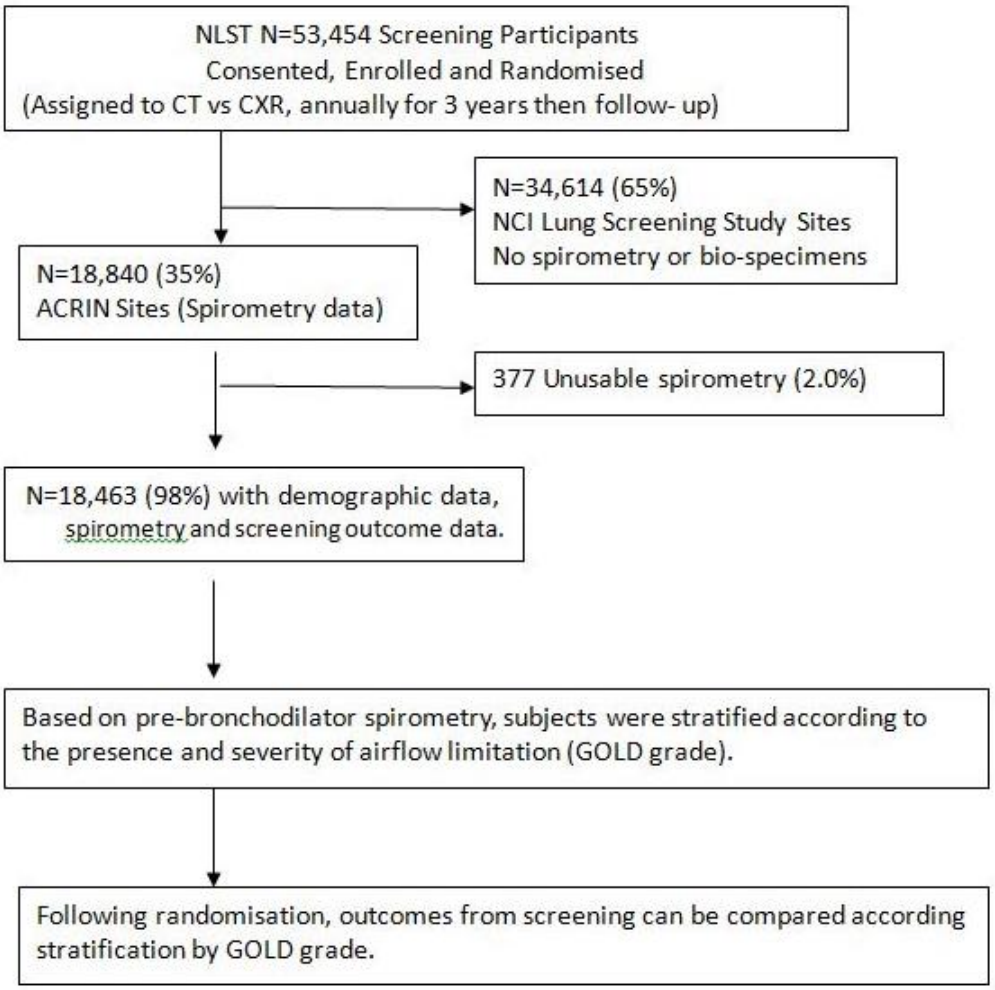
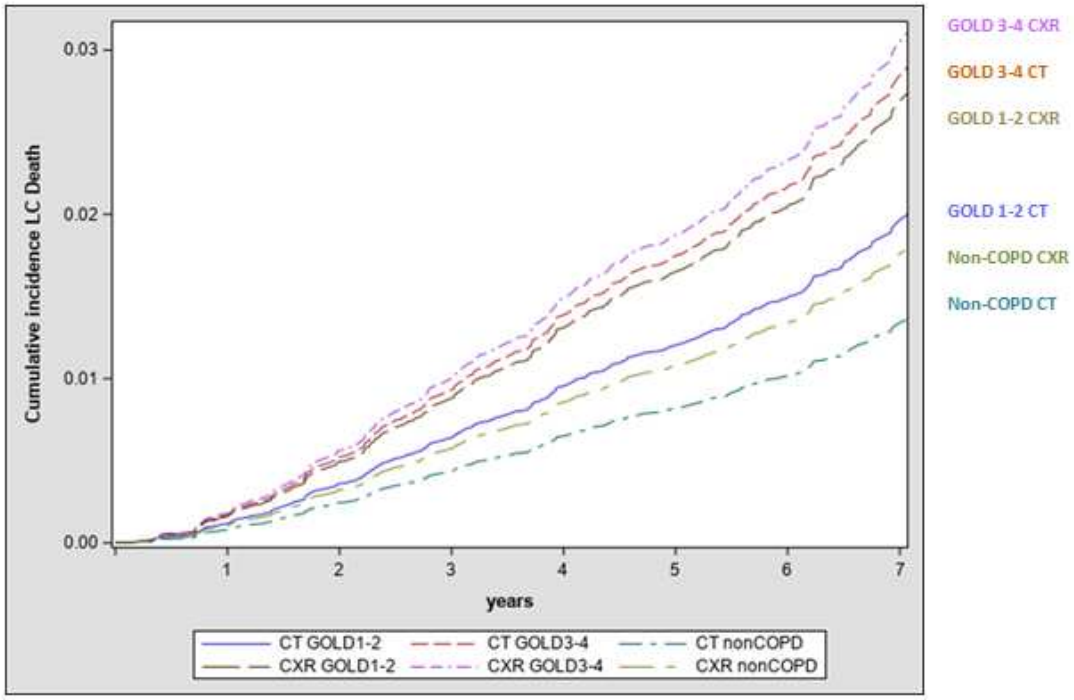
Supplementary Figure 1. Consort figure of the genetic study subgroup from the NLST.



Legend: NLST=National Lung Screening Trial, ACRIN= American College of Radiology, Imaging Network, NCI= National Cancer Institute, NCI=National Cancer Institute, GOLD= Global Initiative of Chronic Lung Disease.

Supplementary Figure 2. Estimated cumulative incidence of death in patients with CT versus CXR screening, according to a competing risk model (Fine and Gray), stratified by GOLD level.



Legend: The superiority of CT over CXR in GOLD 1-2 COPD and non-COPD is reflected in the higher (and diverging) risk of LC death in the CXR arm versus the CT arm as estimated by the competing risk model. This separation is much smaller for those with GOLD 3-4 COPD and replicates the findings in Table 3 suggesting less benefit in this group with severe COPD.

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