Original research

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

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ABSTRACT

Importance Current eligibility criteria for lung cancer (LC) screening are derived from randomised controlled trials and primarily based on age and smoking history. However, the individual benefits of screening are highly variable and potentially attenuated by co-morbidities such as advanced airflow limitation (AL).

Objective To examine the relationship between the presence and severity of AL and screening outcomes.

Methods This was a secondary analysis of 18 463 high-risk smokers, a substudy from the National Lung Screening Trial, who underwent pre-bronchodilator spirometry at baseline and median follow-up of 6.1 years. We used descriptive statistics and a competing risk proportional hazards model to examine differences in screening outcomes by chronic obstructive pulmonary disease severity group.

Results The risk of developing LC increased with worsening AL (effect size=0.34, p<0.0001), as did the risk of dying of LC (effect size=0.35, p<0.0001). While those with severe AL (Global Initiative for Obstructive Lung Disease, GOLD grade 3–4) had the highest risk of LC and the highest LC mortality, they also had fewer adenocarcinomas (effect size=−0.20, p=0.008) and a lower surgery rate (effect size=−0.16, p=0.014) despite comparable staging, and greater non-LC mortality relative to LC mortality (effect size=0.30, p<0.0001). In participants with no AL, screening with CT was associated with a significant reduction in LC deaths relative to chest X-ray (30.3%, 95% CI 4.5% to 49.2%, p<0.05). The clinically relevant but attenuated reduction in those with AL (18.5%, 95% CI −8.4% to 38.7%, p>0.05) could be attributed to GOLD 3–4, where no appreciable mortality reduction was observed.

Conclusion Despite a greater risk of LC, severe AL was not associated with any apparent reduction in LC mortality following screening.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Currently recommended eligibility criteria for lung cancer (LC) screening target those at greatest risk based on age and smoking history criteria. While this helps identify those at greatest risk of LC, it also identifies those most likely to have chronic obstructive pulmonary disease (COPD). While it is accepted that worsening airflow limitation (AL) (or COPD) confers a greater risk of LC, the question arises 'Are the benefits from screening those with severe AL comparable to those with mild-to-moderate AL or normal lung function?'

WHAT THIS STUDY ADDS

⇒ In this secondary analysis of 18 643 high-risk smokers from the National Lung Screening Trial, we found that although those with severe or very severe AL (Global Initiative for Obstructive Lung Disease, GOLD grade 3–4) have the highest risk for LC they also have lower surgical rates (despite comparable staging), more aggressive histology and higher rates of non-LC deaths. We suggest that these factors may contribute to an absence of any apparent reduction in LC mortality in this group following screening ('poor responders') and that their exclusion appears to improve screening efficiency.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Current strategies to optimise LC screening focus primarily on increasing screening efficiency through improved risk prediction. However, these risk-based approaches also enrich for some comorbid diseases including severe COPD. While this group has the greatest risk of LC, this study shows they develop LC of a more aggressive histology, are less likely to undergo surgery and are more likely to die of non-LC causes (competing cause of death). The results of this study suggest the risk–benefit of screening for LC may be marginal for those with severe AL (GOLD 3–4) despite being at greatest risk (ie, is not linear). It also suggests that spirometric assessment may help improve screening efficiency by identifying those for whom the benefits of screening may be outweighed by the harms.

INTRODUCTION

Following the findings of three randomised controlled trials,[1–3] annual CT screening for lung cancer (LC) is now more widely recommended in both the USA and Europe.[4 5] While these studies reported relative risk reductions in LC specific mortality of between 20% and 33%, reduction in all-cause mortality was lower (0%–17% range).[1–3] One potential explanation for this observation is the diluting effect of 'competing cause of death' on reducing overall mortality.[6] In other words, while low-dose CT screening reduces deaths from LC, the benefit for all-cause mortality

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is attenuated by mortality from other smoking-related deaths, notably cardiorespiratory disease.[7–10] Competing cause of death has been defined as 'a failure to achieve improved life expectancy by preventing death from one disease due to death from another cause.'[11] This concept is particularly relevant for LC because, relative to other screening populations, LC screening involves older heavy smokers for whom overall background morbidity and mortality is higher.[6] This is due to coexisting smoking-related diseases, primarily chronic obstructive pulmonary disease (COPD) and cardiovascular disease.[6–10] The impact of comorbid disease and premature death on LC screening outcomes is now the subject of considerable interest.[9 12–14] because the benefit of screening may be diluted.[15]

Studies have previously shown that airflow limitation (spirometric defined COPD), affects between 30% and 60% of those enrolled for LC screening.[16–19] Airflow limitation is a marker for premature death from all causes[20] and found to be unrecognised in 35%–70% of screening participants when spirometry is routinely performed.[16–19] Although worsening airflow limitation increases the risk of developing LC in the National Lung Screening Trial (NLST),[21] in a preliminary analysis, we observed that it was also associated with an almost halving in lung-cancer specific mortality relative to those with normal lung function.[22] We propose that the increased risk of LC associated with worsening airflow limitation is also associated with a greater risk of dying from a cause other than LC.[6 12] We and others have also observed that LC in smokers with airflow limitation may be more aggressive with more squamous cell and less adenocarcinoma subtypes (histology shift).[16 23] This raises two questions, 'As airflow limitation worsens, is there a differential effect on LC-specific mortality relative to other causes of death?' and 'How might the presence of severe airflow limitation attenuate the benefits of CT screening?'

In this secondary analysis of the American College of Radiology Imaging Network (ACRIN) subcohort of the NLST participants (N=18 463), where baseline spirometry was available and the risk of LC could be estimated, we undertook this study to examine the relationship between the presence and severity of airflow limitation and outcomes from screening.

METHODS

Subjects

The recruitment and study design of the full NLST, involving 53 452 screening participants has been described elsewhere.[1] In the ACRIN subcohort of the NLST, which included participants from 23 screening centres (N=18 840), demographic data were collected through an extensive questionnaire and prebronchodilator pulmonary function tests recorded at baseline (online supplementary methods and supplementary figure 1).

Clinical and demographic variables

Demographic variables and clinical variables outlining the subject characteristics at baseline (N=18 463), and prospectively diagnosed LC characteristics (N=785), are described in detail in online supplementary methods.

Screening outcomes

- LC cases: included those diagnosed during the trial (N=757) or during postmortem examination (N=28).
- Stage shift: the proportion of patients diagnosed with LC in stage 1 or 2 was determined for each screening group.
- LC surgery: the proportion of LC cases that underwent surgery.
- Mortality: LC and non-LC deaths during follow-up as ascertained through review of clinical records and death certification (total=1372).

Statistical analysis

We first determined summary statistics for clinical and demographic variables and study outcomes by COPD severity groups, and tested for overall associations by using χ^2, Fisher's exact or analysis of variance tests, as appropriate. We also reported effect sizes as Goodman and Kruskal's gamma statistic, a measure of rank correlation with a range of (−1 to 1); values closer to 0 indicate lower association between compared variables (see online supplementary section). We next compared absolute differences among LC cases between screening groups (CT vs chest X-ray (CXR)) within each COPD severity group for: (1) stage 1–2 diagnoses, (2) adenocarcinoma histology, (3) surgical treatment following diagnosis and (4) LC death. These absolute differences were expressed as percentages with 95% CIs. We then calculated several LC death statistics and their 95% CI from the full screening population by comparing screening groups within each COPD severity level (see online supplementary methods). In further online supplementary analyses, we conducted competing risk proportional hazards analyses (Fine and Gray subdistributional models—see Supplementary Methods). All analyses were performed using SAS (V.9.4, SAS Institute).

RESULTS

Baseline comparison of demographic and clinical variables

From the total cohort of 18 643 NLST subjects, there were 12 303 controls with no airflow limitation (66.6%), 1499 had Global Initiative for Obstructive Lung Disease (GOLD) 1 (8.1%), 3412 had GOLD 2 (18.5%) and 1249 had GOLD 3–4 (6.8%), airflow limitation (table 1). Airflow limitation was associated with the following differences: older age, being male, greater duration of smoking, greater pack years and greater rate of current smoking. Worsening airflow limitation was associated with modestly reduced body mass index. GOLD 3–4 disease was associated with the greatest cigarettes per day, pack years, history of COPD; lowest educational level, worst lung function and the most respiratory comorbid disease. GOLD 3–4 was also associated with the most heart disease. Only 56% of those with GOLD 3–4 disease reported a prior diagnosis of COPD compared with 18% and 30% in those with GOLD 1 and 2, respectively (table 1). Airflow limitation was not associated with ethnicity, or family history of LC.

LC and mortality outcomes

From the total cohort, the risk of developing LC increased with worsening airflow limitation (effect size=0.34, p<0.0001) (table 2, figure 1). Similarly, the risk of dying of LC also increased according to worsening airflow limitation (effect size=0.35, p<0.0001). GOLD 3–4 patients had the highest rates of LC diagnosis and LC mortality. With increasing airflow limitation, there was a decreasing prevalence of adenocarcinoma (effect size=−0.20, p=0.008) and less surgery (effect size=−0.16, p=0.014), despite comparable staging. Compared with controls, the GOLD 3–4 COPD group was associated with a significantly greater prevalence of non-small cell lung carcinoma–not otherwise specified (NSCLC-NOS) histology and less adenocarcinoma (table 2 and online supplemental table 1). There was no effect on stage shift by COPD severity. GOLD 3–4 COPD was associated with a lower prevalence of LCs in the prevalent (baseline, T0) scan, less screen-detected LCs and greater LC prevalence during the follow-up (non-screening) interval but these differences were not statistically different. With increasing airflow limitation,

Table 1 Baseline demographic variables according to the presence and severity of airflow limitation

	Non-COPD controls (no airflow limitation)	COPD GOLD 1	COPD GOLD 2	COPD GOLD 3–4	Effect size†	P value‡
N=18 463 (% total)	N=12 303 (66.6)	N=1499 (8.1)	N=3412 (18.5)	N=1249 (6.8)		
Demographic and risk variables						
Race (% white)	11332 (92)	1401 (93.5)	3203 (93.9)	1147 (92)	0.07	0.16
Mean age -years	61	62	63	63	0.17	<0.0001
Male sex (%)	6537 (53.1)	965 (64.4)	1983 (58.1)	722 (57.8)	−0.10	<0.0001
Current smoker (%)	5803 (47.2)	853 (56.9)	1971 (57.8)	661 (52.9)	0.16	<0.0001
Mean pack years	53.7	57.2	59.8	63.6	0.17	<0.0001
Mean cigarettes/day	28	28	28	30	0.06	<0.0001
Mean years quit	4	3	3	3	−0.15	<0.0001
Mean smoking duration years	39	42	42	43	0.23	<0.0001
Family history of lung cancer (%)	2866 (23.3)	358 23.9)	790 (23.2)	306 (24.5)	0.009	0.74
Personal history of COPD* (%)	1729 (14.1)	262 (17.5)	1019 (29.9)	696 (55.7)	0.48	<0.0001
Mean body mass index	28.4	25.9	26.9	26.9	−0.18	<0.0001
Education level (%)					−0.08	<0.0001
► High school or less	3436 (27.9)	430 (28.7)	1133 (33.2)	477 (38.2)		
► Post high school training	1418 (11.5)	180 (12.0)	415 (12.2)	150 (12.0)		
► Some college	2876 (23.4)	317 (21.1)	705 (20.7)	275 (22.0)		
► College graduate	2111 (17.25)	302 (20.1)	548 (16.1)	182 (14.6)		
► Postgraduate/professional	2132 (17.3)	241 (16.1)	511 (15.0)	129 (10.3)		
► Other/unknown	330 (2.7)	29 (1.9)	100 (2.9)	36 (2.9)		
Lung function/airflow limitation						
Mean FEV_1 % predicted	89.0	90.7	65.3	38.6	−0.70	<0.0001
Mean FEV_1/FVC	77.7	64.9	61.0	48.3	−0.95	<0.0001
Comorbid disease (self-reported)						
COPD	406 (3.3)	58 (3.9)	412 (12.1)	368 (29.5)	0.63	<0.0001
Adult asthma	631 (5.1)	59 (3.9)	338 (9.9)	219 (17.5)	0.36	<0.0001
Chronic bronchitis	1117 (9.1)	118 (7.9)	488 (14.3)	348 (27.9)	0.32	<0.0001
Emphysema	535 (4.3)	138 (9.2)	490 (14.4)	444 (35.5)	0.61	<0.0001
Pneumonia	3066 (24.9)	375 (25.0)	989 (29.0)	458 (36.7)	0.12	<0.0001
Heart disease	1589 (12.9)	168 (11.2)	472 (13.8)	207 (16.6)	0.05	0.0002
Hypertension	4511 (36.7)	453 (30.2)	1307 (38.3)	477 (38.2)	0.007	<0.0001
Stroke	359 (2.9)	29 (1.9)	118 (3.5)	44 (3.5)	0.05	0.014
Diabetes	1269 (10.3)	70 (4.7)	281 (8.2)	119 (9.5)	−0.12	<0.0001
Any cancer history	481 (3.9)	56 (3.7)	153(4.5)	53(4.2)	0.04	0.43

*Reported 'yes' to one or more of a past diagnosis of COPD, adult asthma, chronic bronchitis or emphysema.
†Goodman and Kruskal gamma statistic.
‡χ^2, Fisher's exact or ANOVA tests reported, as appropriate.
ANOVA, analysis of variance; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; GOLD, Global Initiative for Obstructive Lung Disease.

the non-LC mortality increased at a greater rate than for LC mortality (figure 1). This divergence was attributed in the main to increasing cardiorespiratory deaths in the GOLD 3–4 group.

Screening outcomes by COPD group

Table 3 includes screening outcomes among LC cases and among the full population by screening group and COPD severity. Group sizes used to support these calculations are also included. Among LC cases, outcomes include absolute changes in stage 1–2 diagnoses, adenocarcinoma histology, surgical treatment following diagnosis and LC death. Among the full population we describe both relative and absolute differences in mortality from LC (see Supplementary Methods).

For the controls (no airflow limitation), randomisation to the CT arm favoured stage shift to early-stage cancers and significant reductions in LC deaths in relative terms (30.3% reduction, 95% CI 4.5% to 49.2%) and absolute terms (4.6 LC deaths averted per 1000 screened, 95% CI 0.4 to 8.4). For those with airflow limitation (GOLD grades 1–4), there was an attenuated benefit in those randomised to CT with a non-significant reduction in LC deaths (18.5% relative reduction, 95% CI −8.4% to 38.7%) relative to CXR. It is notable that screening benefits due to stage shift and LC mortality reduction were reduced as airflow limitation increased. For those with severe or very severe airflow limitation (GOLD 3–4), there was no apparent stage shift, adenocarcinoma histology shift, or reduction in LC mortality; further, there was a negative estimate for number needed to screen (NNS). This contrasts with those with GOLD one airflow limitation with a comparable sample size (and similar powering); figure 2A further illustrates this contrast. We also note that despite lower rates of LC-related surgery with worsening airflow limitation (table 2), there was consistently greater surgery in those randomised to CT relative to CXR in all groups (including GOLD grade 3–4, 47% vs 33%) (table 3). Interestingly, while 47% of LC cases in the CT arm underwent surgery for GOLD 3–4 (table 3, figure 2), there was no meaningful stage

Table 2 Characteristics of LC cases and non-LC mortality stratified by the presence and severity of airflow limitation

	Non-COPD Controls	COPD GOLD 1	COPD GOLD 2	COPD GOLD 3–4	Effect size†	P value‡
N=18 463 (% total)	N=12 303 (66.6)	N=1499 (8.1)	N=3412 (18.5)	N=1249 (6.8)		
LC outcomes*						
LC diagnosis N (% group)	380 (3.1)	78 (5.2)	212 (6.2)	115 (9.2)	0.34	<0.0001
LC death N (% group)	173 (1.4)	45 (3.0)	96 (2.8)	57 (4.6)	0.35	<0.0001
LC lethality	45.5	57.7	45.3	49.6	0.03	0.22
Mean patient years follow-up	6.2 (1.0)	6.2 (1.1)	6.1 (1.2)	5.9 (1.4)	–0.06	<0.0001
LC surgery N (% yes)	211 (55.5)	37 (47.4)	110 (51.9)	44 (38.3)	–0.16	0.014
LC histology N (% LC)						
Small cell	52 (13.7)	11 (14.1)	35 (16.5)	15 (13.0)	0.03	0.78
Squamous cell	72 (18.9)	14 (18.0)	48 (22.6)	31 (27.0)	0.13	0.25
Adenocarcinoma (incl BAC)	174 (45.8)	31 (41.0)	74 (34.9)	37 (30.4)	–0.20	0.008
Non-small cell-NOS	52 (13.7)	14 (18.0)	39 (18.4)	26 (22.6)	0.18	0.11
Large cell	14 (3.7)	5 (6.4)	10 (4.7)	1 (0.87)	–0.09	0.17
Other/unknown	16 (4.2)	2 (2.6)	6 (2.8)	7 (6.1)	0.02	0.48
LC stage N (% LC)						
Stage I-II	182 (47.9)	31 (39.7)	97 (45.8)	55 (47.8)	–0.02	0.61
Stage III	76 (20.0)	18 (23.1)	53 (25.0)	21 (18.3)	0.04	0.41
Stage IV	103 (27.1)	25 (32.1)	52 (24.5)	30 (26.1)	–0.03	0.63
Occult carcinoma/unknown	19 (5.0)	4 (5.1)	10 (4.7)	9 (7.8)	0.09	0.64
Screen detection N (%LC)						
T0 detection (first yr screening)	95 (25.0)	15 (19.2)	48 (22.6)	21 (18.3)	–0.10	0.40
T0-T2 screen year detection	228 (60.0)	52 (66.7)	128 (60.4)	60 (52.2)	–0.06	0.23
T3-T7 (folowup years detection)	152 (40.0)	26 (33.3)	84 (39.6)	55 (47.8)	0.06	
LC screen detected	187 (49.2)	39 (50.0)	102 (48.1)	49 (42.6)	–0.06	0.64
LC interval detection	41 (10.8)	13 (16.7)	26 (12.3)	11 (9.6)	0.009	0.43
LC follow-up detection	152 (40.0)	26 (33.3)	84 (39.6)	55 (47.8)	0.06	0.23
Non-LC mortality						
Total deaths (N) - per 100 screened (%)	706 (5.7)	118 (7.9)	332 (9.7)	216 (17.3)	0.32	<0.0001
Non-LC deaths (N) -per 100 screened (%)	533 (4.3)	73 (4.9)	236 (6.9)	159 (12.7)	0.30	<0.0001
Cardiovascular (CVD) deaths (N) -per 100 screened (%)	170 (1.4)	21 (1.4)	91 (2.7)	42 (3.4)	0.29	<0.0001
Respiratory deaths (N) -per 100 screened (%)	35 (0.28)	2 (0.13)	23 (0.67)	61 (4.9)	0.70	<0.0001
Other cancer deaths (N) -per 100 screened (%)	157 (1.3)	25 (1.7)	70 (2.1)	23 (1.8)	0.18	0.006
Other deaths (N) -per 100 screened (%)	171 (1.4)	25 (1.7)	52 (1.5)	33 (2.6%)	0.14	0.012

*Includes LCs diagnosed at postmortem.
†Goodman and Kruskal gamma statistic.
‡χ^2, Fisher's exact or ANOVA tests reported, as appropriate.
ANOVA, analysis of variance; BAC, bronchioloalveolar cancers; COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Obstructive Lung Disease; LC, lung cancer; NOS, not otherwise specified.

shift and no apparent reduction in LC mortality. If this group (GOLD 3–4) were excluded from screening on the basis that harms may outweigh the benefits (figure 2B), we found screening efficiency marginally increased as indicated by a greater relative reduction in LC mortality: 29.0% (95% CI 10.6% to 43.7%) up from 24.9% in the full group (95% CI 7.1% to 39.2%), and a reduced NNS to avert one LC death: 174, 95% CI (57 to 290) down from 190, 95% CI (50 to 329) in the full group.

Factors contributing to LC deaths

We found similar results from a competing risk proportional hazards model (Fine and Gray) for LC death, adjusted for important clinical and demographic predictors (Supplementary Methods and table 2). Although the interaction between screening arm and COPD severity was not significant in the model (p=0.53), the stratified results indicated a trend towards CT screening advantage for the non-COPD group (HR 0.76 95% CI 0.56 to 1.03, p=0.073) and the GOLD 1–2 group (HR 0.73, 95% CI 0.52 to 1.02, p=0.063), but statistically non-significant results for the GOLD 3–4 group (online supplemental table 2). We conclude from the model that age, pack years, years since quitting, history of self-reported COPD, emphysema, asthma and diabetes all contribute to dying from LC. The cumulative incidence function plots (online supplemental figure 2) further illustrate the increasing

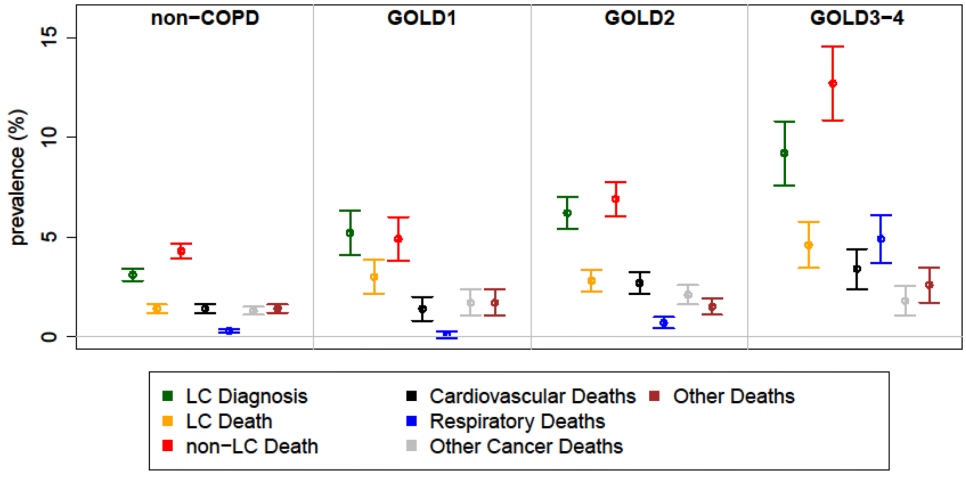

Figure 1 Lung cancer prevalence and cause-specific mortality per 100 screened according to gold grade (data from table 2). The increase in non-lung cancer deaths (red) is steeper than for lung cancer deaths (orange) hence divergence in overall mortality across worsening airflow limitation. Worsening airflow limitation is associated with increases in cause-specific mortality; notably cardiovascular (black) and respiratory deaths (blue) were greatest in those with GOLD 3–4. GOLD, Global Initiative for Obstructive Lung Disease.

and diverging risk for LC death as COPD severity increases, with a corresponding decline in screening benefit.

DISCUSSION

In this analysis of the ACRIN arm of the NLST, including 18 463 high-risk subjects, we have examined the effect of underlying airflow limitation on outcomes from LC screening. Although airflow limitation is associated with an increased risk of LC,[22] in this study having severe airflow limitation (GOLD 3–4) was associated with no apparent benefit from CT-based LC screening. Specifically, the reduced improvement in LC cancer mortality we report in the total group with airflow limitation, 18% vs 30% in those with no airflow limitation, could be attributed almost entirely to those with the most severe airflow obstruction (GOLD 3–4 grade) and greatest respiratory comorbidity. While GOLD 3–4 subjects represented nearly 7% of the entire ACRIN cohort, they accounted for 14.6% of LCs. We note that for GOLD 3–4 subjects, 47% of the LC identified in the CT arm underwent surgery although no benefit from screening and treatment was observed. The basis of this finding likely stems from one or a combination of factors related to the screening subject or their LC.[6] Despite GOLD 3–4 screening participants having greater respiratory-related comorbid disease and greater cardiorespiratory deaths, only 56% were aware they had COPD. This group also developed LCs that were less likely to be detected by screening, were of a more aggressive histology (more squamous cell and NSCLC-NOS but less adenocarcinomas),[16 23 24] and experienced lower surgical rates for their cancers. These LC characteristics likely underpin the lack of stage shift in the CT arm relative to CXR in this group. Collectively, these findings demonstrate that among those with GOLD 3–4 airflow limitation, and at greatest risk of LC, nearly half underwent work-up and surgery yet no apparent benefit from screening was observed. In the clinical setting where LC screening is targeted to those who stand to gain the most from screening,[19] spirometry and respiratory comorbidity may help identify those for whom screening may expose them to greater harm than benefit.

One important implication of this finding is that the relationship between risk and benefit from screening is not linear.[6 12] Specifically, those at greatest risk of LC according to their spirometry,[21] actually do not benefit most from screening. In fact, this study suggests that spirometric assessment of smokers eligible for screening will identify those with GOLD 3–4 airflow limitation who appear to be 'poor responders' to LC screening and for whom screening may be more harmful than beneficial. A second implication of this study is that including spirometry during screening may provide very useful information for the screening participant and their physician by identifying undiagnosed COPD or quantifying severity of airflow limitation.[6 16–19] A third and more important implication of this finding is that to optimise LC screening benefits (and efficiency) it might be better to focus on those with the best outcomes rather than focus solely on those at greatest risk of LC. LC screening is quite different to other cancer screening programmes because those eligible for screening are enriched to have the greatest risk but will include many with a shortened life expectancy.[6–12] As pulmonary function tests are also closely linked to life expectancy,[20] better reflecting biological age rather than chronological age, their routine use in LC screening may help identify who derives the least benefit from screening. For these reasons, we propose that quantifying airflow limitation provides useful information about the outcomes (responsiveness) and risks for smokers undergoing LC screening.[6 13 14]

There are several factors that might contribute to the poor outcomes in NLST subjects with GOLD 3–4 disease. Consistent with studies in non-screened LC, we have shown airflow limitation in screened subjects was associated with more aggressive types of LC, specifically squamous cell and NSCLC-NOS subtypes.[16 23–25] We and others have linked pre-existing airflow limitation in LC subjects with shorter volume doubling times.[26 27] This may mean that the most aggressive LCs are less amenable to detection and successful treatment through screening. Our results support this by showing those with GOLD 3–4 had fewer screen-detected cancers and less surgery overall (independent of screening arm). These differences may explain the lack of stage shift in this group when comparing CT with CXR and certainly also explains the lack of benefit in reducing LC mortality. Another possible explanation for there being no benefit from screening in GOLD 3–4 subjects is that they experienced much higher non-LC deaths relative to their LC death rate (divergence in figure 1). This could be attributed to the higher rates of pre-existing comorbid respiratory disease and high rates of cardiorespiratory death during screening.[6 25] When life expectancy is factored into assessing the benefits of LC screening,

Table 3 Outcomes following randomisation to the CT and CXR arms according to the presence and/or severity of airflow limitation (GOLD grade)

Group sizes	Non-COPD controls		COPD GOLD 1		COPD GOLD 2		COPD GOLD 3–4	
COPD group sizes (%) N=18 463 total	N=12 303 (66.6)		N=1499 (8.1)		N=3412 (18.5)		N=1249 (6.8)	
CT versus CXR group size (full pop.)	CT N=6195	CXR N=6108	CT N=729	CXR N=770	CT N=1671	CXR N=1741	CT N=629	CXR N=620
LC diagnosed‡	196	168	42	34	97	111	57	52
Total patient-years follow-up for LC	37 548	37 292	4380	4684	9787	10 271	3554	3450
Mean patient-years follow-up (SD)	6.2 (1.0)		6.2 (1.1)		6.1 (1.2)		5.9 (1.4)	
Absolute changes among LC diagnosis population‡								
Stage 1–2 LC	114 (58.2%)	68 (40.4%)	22 (52.4%)	9 (26.4%)	49 (50.5%)	48 (43.2%)	27 (47.4%)	28 (53.8%)
Stage shift favouring CT	17.7%* (7.0%, 27.3%)		25.9%* (2.1%, 44.4%)		7.3% (–7.3%, 19.9%)		–6.5% (–23.4%, 14.1%)	
Adenocarcinoma Histology† N (%)	106 54.1%	68 40.5%	21 50.0%	11 32.4%	36 37.1%	38 34.2%	16 28.1%	16 28.1%
Adenocarcinoma histology shift favouring CT (95% CI)	13.6%* (2.8% to 23.2%)		17.6% (–6.8% to 36.8%)		2.9% (–11.1% to 15.0%)		–8.5% (–27.8% to 7.2%)	
LC surgical rate in CT versus CXR arm N (%)	130 (66.3%)	81 (48.2%)	23 (54.8%)	14 (41.2%)	56 (57.7%)	54 (48.6%)	27 (47.4%)	17 (32.7%)
Surgical rate favouring CT (95% CI)	+18.1%* (7.5% to 27.6%)		+13.6% (–11.4% to 33.3%)		+9.1% (–5.4% to 21.6%)		+14.7% (–5.3% to 31.0%)	
LC death rate in CT versus CXR arm N (%)‡	65 (33.1%)	92 (54.7%)	18 (42.9%)	25 (73.5%)	38 (39.2%)	54 (48.6%)	26 (45.6%)	25 (48.1%)
LC death rate favouring CT (95% CI)	–21.6%* (–31.1% to –11.0%)		–30.7%* (–49.1% to –6.9%)		–9.5% (–21.9% to 4.9%)		–2.5% (–19.4% to 18.1%)	
Relative and absolute changes among full screening population								
Relative reduction† in LC deaths (% reduction)	–30.3%* (–49.2%, –4.5%)		–24.0% (–58.2%, 38.2%)		–26.7% (–51.3%, 10.4%)		+2.5% (–40.1%, 75.5%)	
Absolute LC deaths averted/1000 patients screened (95% CI)	+4.6/1000* (0.4 to 8.4)		+7.8/1000 (–10.4 to 23.3)		+8.3/1000 (–3.1 to 18.5)		–1.0/1000 (–24.6 to 19.3)	
Absolute LC deaths averted per COPD group (cumul. % of total)	–27 (54%)		–7 (68%)		–16 (100%)		+1 (excess)	
LC deaths averted /1000 patient years (95% CI)	0.7/1000* (0.1 to 1.4)		1.2/1000 (–1.4 to 4.3)		1.4/1000 (–0.4 to 3.3)		–0.1/1000 (–3.8 to 4.2)	
OR of LC death (95% CI)‡	0.69* (0.50 to 0.95)		0.75 (0.41 to 1.39)		0.72 (0.47 to 1.10)		1.03 (0.58 to 1.79)	
NNS to avert one LC death (95% CI)	219 (29 to 409)		129 (–150 to 407)		120 (–37 to 279)		–987 (–20 408 to 22 383)	
Controls versus GOLD 1–4	Non-COPD controls N=12 303 (66.6%)		COPD GOLD 1–4 N=6160 (33.4%)					
Relative reduction† in LC deaths in CT vs CXR (% reduction)	–30.3%* (–49.2%, –4.5)		–18.5% (–38.7%, 8.4%)					
Absolute LC deaths averted with CT Risk Difference (95% CI)	+4.6/1000* (0.6 to 8.5)		+6.1/1000 (–2.4 to 14.7)					
Controls versus GOLD 1–2	Non-COPD Controls N=12 303 (66.6%)		COPD GOLD 1–2 (excluding GOLD 3–4) N=4911 (26.6%)					
Relative reduction† in LC deaths in CT vs CXR (% reduction)	–30.3%* (–49.2%, –4.5)		–25.8% (–47.1%, +3.9%)					
Absolute LC deaths averted with CT Risk Difference (95% CI)	+4.6/1000* (0.6 to 8.5)		+8.1/1000 (–0.6 to +17.7)					

P<0.05 in bold and shaded green. Brown shaded results are not statistically significant.
NNS is 190 in the whole cohort (95% CI 50 to 329).
The OR of LC death for GOLD groups 1 and 2 is 0.74 (95% CI 0.52 to 1.04) and NNS=123 (95% CI –15 to 261).
*Excludes LCs diagnosed at post-mortem (N=28).
†Adenocarcinoma (including BAC).
‡Excludes lung cancer cases diagnosed at post-mortem (N=28).
BAC, bronchioloalveolar cancer; COPD, chronic obstructive pulmonary disease; CXR, chest radiograph; GOLD, Global Initiative for Obstructive Lung Disease; LC, lung cancer; NNS, number needed to screen.

it appears the best outcomes are achieved when those with intermediate risk are targeted.[6 12 28] This combines increased risk of LC with greater relative reduction in LC deaths and greater long-term survival.

A key result from this study is that of the 49 LC deaths averted by using CT-based screening in the whole cohort, 27 deaths were averted in those with normal lung function and 23 deaths were averted in those with GOLD 1–2 disease (table 3). There

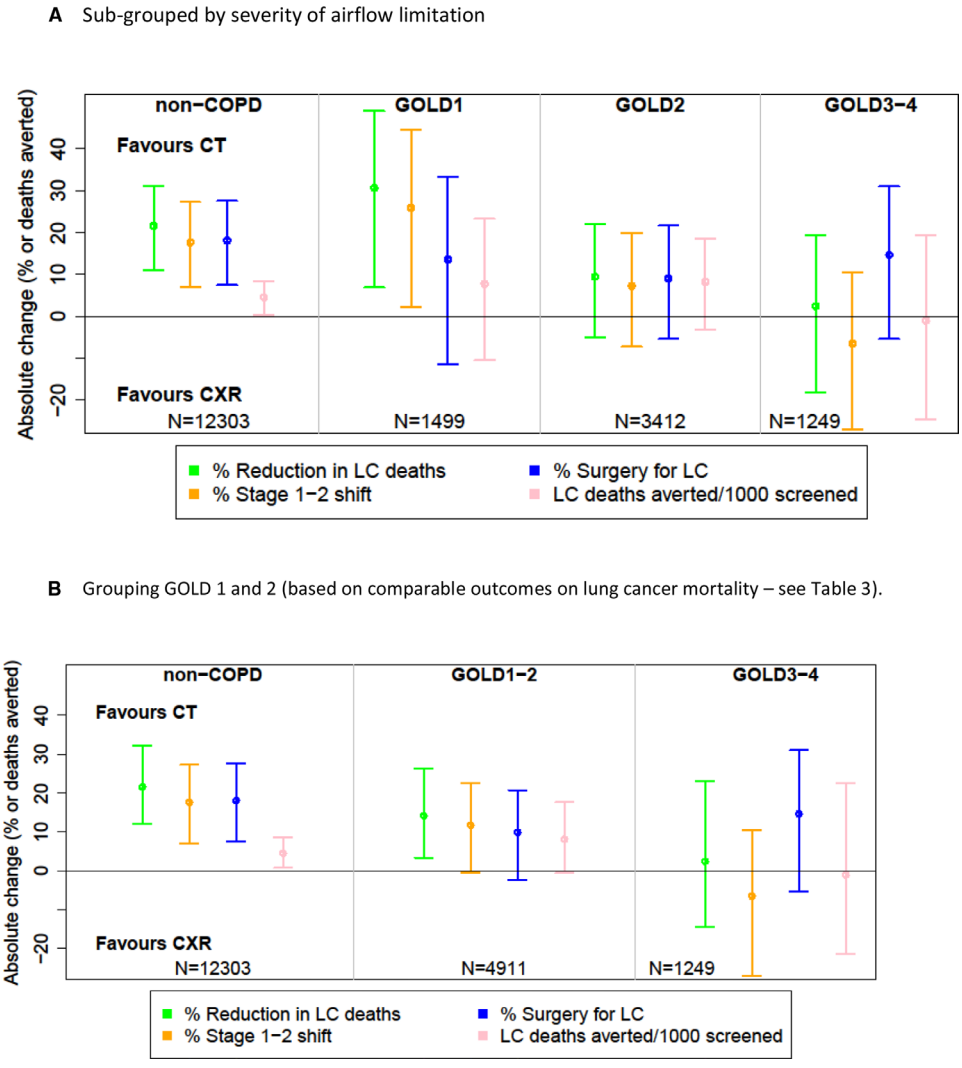

Figure 2 Screening outcomes favouring randomisation to the CT arm relative to the CXR arm in the NLST according to gold grade (data from table 3). (A) Subgrouped by severity of airflow limitation (B) grouping GOLD 1 and 2 (based on comparable outcomes on lung cancer mortality—see table 3). GOLD groups 1 and 2 have been combined on the basis the lung cancer mortality benefit favouring CT are comparable; ORs of 0.75 (95% CI 0.41 to 1.39) and 0.72 (95% CI 0.47 to 1.10) and absolute lung cancer deaths averted per 1000 of 7.8 (95% CI −10.4 to 23.3) and 8.3 (95% CI −3.1 to 18.5) for gold groups 1 and 2, respectively. CXR, chest X-ray; GOLD, Global Initiative for Obstructive Lung Disease; NLST, National Lung Screening Trial.

was one excess LC death in the CT arm over the CXR arm for those with GOLD 3–4 disease. Thus, in our secondary analysis, we found no benefit in screening for LC in the latter group. In fact, screening was more efficient (lower NNS) when this group of poor responders was excluded. We note the prevalence of GOLD 3–4 airflow limitation was 7% in the NLST-ACRIN study and between 4% and 8% in other screening studies.[17–19] Given there was likely to be greater harm from the work up and treatment of LCs in those with severe COPD,[29] we suggest the net harm may outweigh the benefit. This argues strongly for identifying eligible smokers with GOLD 3–4 disease and greater consideration of whether this group should be offered surgery following screening. While stereotactic-based radiotherapy has been shown in observational studies to achieve comparable short-term survival to those receiving surgery in unscreened LC patients with GOLD 3–4 COPD,[30] the long-term benefits relative to complications from screening and investigating this group remains less clear.[8] Prospective studies comparing mortality reduction according to lung function are needed to confirm our findings. We suggest that as the risk of LC increases, the potential for doing harm may also increase when selection criteria for screening targets only those at greatest risk. This demonstrates the greater utility of an outcomes-based approach over a risk-based approach to screening. In an outcomes-based approach, smokers eligible for screening based on age and pack years criteria are reassessed with regards to their 'responsiveness' to LC screening according to comorbid diseases like severe COPD where the impact on screening outcomes, and thus the benefit to harm ratio, are significantly altered.

There are several strengths and weaknesses to this study. This subanalysis included data for over 18 000 screening subjects from 23 different sites who underwent baseline spirometry and followed for a median of 6.1 years. Despite this large study size, the number of LCs diagnosed during this study was only 785 and this significantly limited our ability to determine what variables contributed most to the poor outcomes we report for the GOLD 3–4 group. This means that after stratification by GOLD grade, our analyses were underpowered. That said, the primary clinical end point of LC death allowed us to examine differences in outcome by screening. Other weakness includes no data on biopsy rates, procedural complications from nodule work up or

perioperative care. This may be important as others have shown that subjects with COPD have more nodules to follow-up, greater complications during nodule workup and more complications from surgery.[29] Lastly, we note the NLST cohort may not best represent those undergoing screening for LC in community-based studies and that ongoing prospective studies comparing outcomes are required to confirm our findings.

In conclusion, this study demonstrates that increasing risk of LC does not necessarily translate into increasing benefit from screening in a simple linear relationship. More importantly the findings show routine use of spirometry helps identify those with severe airflow limitation conferring a reduced life expectancy, greater risk for aggressive LC and greater mortality risk from non-LC causes. These observations suggest that routine use of spirometry may help identify this largely unrecognised but important 'poor responder' subgroup for whom LC screening may cause more harm than benefit.

Contributors RPY and RJS contributed to the conception and design; acquisition, analysis and interpretation; drafting and review for important intellectual content and final approval of the manuscript. GS contributed to the analysis and interpretation; drafting and review for important intellectual content and final approval of the manuscript. RCW and GDG contributed to bio statistical analysis, drafting, review and final approval of the manuscript.

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Patient consent for publication Not applicable.

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

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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

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.

Young RP, *et al. Thorax* 2022;0:1–9. doi: 10.1136/thorax-2022-219334

Supplementary References

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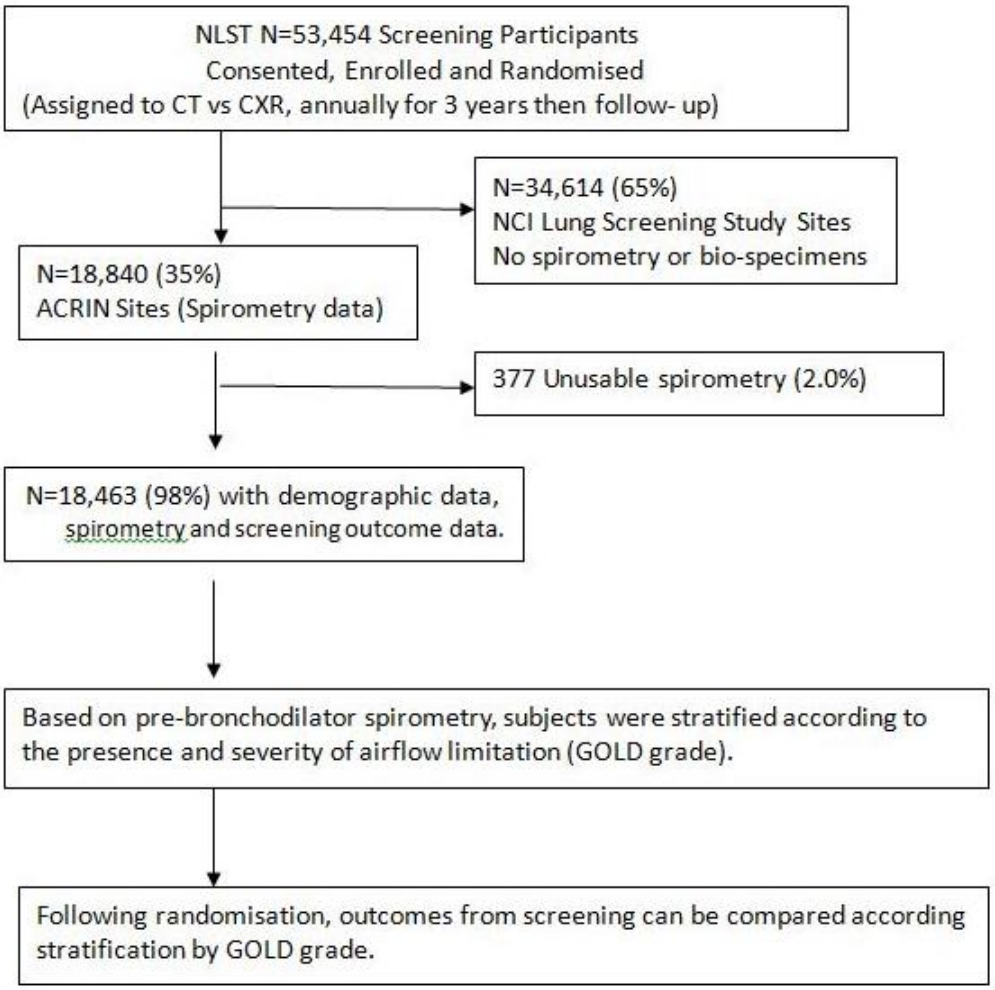
Supplementary Table 2. Competing risk model‡ (Hazard Ratio) analyses for lung cancer death after screening

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.

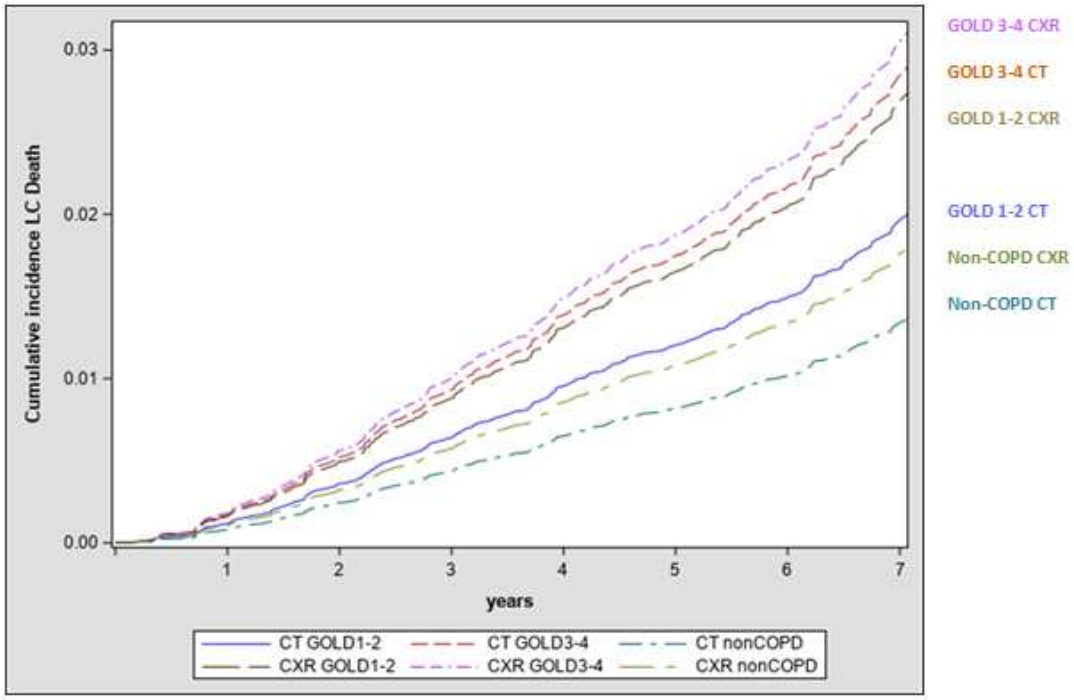
$^{\Phi}$Legend: We combined GOLD 1 and 2 because they had very similar rates of LC incidence and death in our initial analysis (Table 2) and very similar screening outcomes favouring CT, specifically; relative reduction in lung cancer death (24% and 27%), absolute lung cancer deaths averted per 1000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

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.