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Interstitial lung abnormalities are associated with increased mortality in smokers

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ABSTRACT

Objective: The aim of this study was to investigate whether smokers with incidental findings of interstitial lung abnormalities have an increased mortality during long-term follow-up, and review the contributing causes of death.

Methods: Baseline CT scans of 1990 participants from the Danish Lung Cancer Screening Trial were qualitatively assessed for predefined interstitial lung abnormalities of any severity. Inclusion criteria for this lung cancer screening trial included current or former smoking, > 20 pack-years, and age 50–70 years. Patients were followed up for up to 12 years.

Results: We found interstitial lung abnormalities in 332 participants (16.7%). Interstitial lung abnormalities were associated with increased all-cause mortality in the full cohort (HR: 2.0, 95% CI: 1.4–2.7, $P < 0.001$) and in lung cancer-free participants (HR: 1.6, 95% CI: 1.1–2.4, $P = 0.007$). The findings were associated with death from lung cancer (HR: 3.2, 95% CI: 1.7–6.2, $P < 0.001$) and non-pulmonary malignancies (HR: 2.1, 95% CI: 1.1–4.0, $P = 0.02$). Participants with fibrotic and non-fibrotic interstitial lung abnormalities had similar survival.

Conclusion: Interstitial lung abnormalities were common in this lung cancer screening population of relatively healthy smokers and were associated with mortality regardless of the interstitial morphological phenotype. The increased mortality was partly due to an association with lung cancer and non-pulmonary malignancies.

1. Introduction

Interstitial lung abnormalities (ILA) are areas of increased lung density visible on computed tomography (CT) of the lung in individuals with no known interstitial lung disease. These radiological findings, including ground-glass opacities, reticulation, nodular patterns, and honeycombing, are also present in several interstitial lung diseases, such as idiopathic pulmonary fibrosis (IPF) and can precede the onset of symptoms by several years [1,2]. However, not all ILA develop into symptomatic lung disease and the clinical implications of ILA are still the subject of ongoing research.

ILA have been detected in smokers and participants of lung cancer screening trials, and fibrotic ILA have been shown to progress radiologically within 2–4 years of follow-up [3–7]. The radiological findings of ILA are associated with measurable changes in lung volume, gas exchange, and exercise capacity [5,7,8].

In previous reports, ILA have been found to be associated with greater risk of all-cause mortality [9,10], but the cause of this association is not entirely clear. A tempting explanation could be the development of some ILA into clinical interstitial lung disease or lung cancer, but these possible scenarios remain to be proven.

The aim of this study was to investigate whether healthy smokers with incidental findings of interstitial lung abnormalities have an increased mortality during long-term follow-up, and classify the contributing causes of death.

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2. Methods

2.1. Study population

All participants in the intervention arm of the Danish Lung Cancer Screening Trial (DLCST) were eligible for this registry-based follow-up study. Details of the methods of the DLCST, including criteria of eligibility, have been published previously and are briefly described below [11]. The DLCST was a 4- year, 5-round prospective randomized controlled screening trial. From 2004 to 2006, 4104 men and women aged 50–70 years with a smoking history of at least 20 pack-years were included in the study. Former smokers had to have quit after the age of 50 years and within the previous 10 years. Baseline FEV_1 had to be ≥ 30% of the predicted value and participants had to be able to climb two flights of stairs (total of 36 steps) without pausing. Exclusion criteria were weight > 130 kg, history of cancer diagnosis and treatment, lung tuberculosis, shortened life expectancy < 10 years, and chest CT screening during the past year for any reason. Participants with suspected malignant findings were immediately referred for further investigations. However, participants with interstitial findings were not systematically followed up for either diagnosis or treatment. The DLCST was approved by the Ethics Committee of Copenhagen County and fully funded by the Danish Ministry of Interior and Health. Approval of data management in the trial was obtained from the Danish Data Protection Agency. All participants provided written informed consent and the study was conducted according to the principles of the Declaration of Helsinki.

In the present follow-up study, participants were included in the survival analysis provided they were randomized to the screening arm and had an evaluated CT scan available (n = 1990). Seventy participants developed lung cancer during follow-up. Survival analysis was performed both with the entire cohort and with lung cancer free participants (n = 1920), to unmask possible confounding by this co-morbidity (Fig. 1). All participants were included in the cause of death analysis, to ensure completeness of data.

2.2. Imaging and image review

Baseline scans from the DLCST were used for this follow-up study. Details about the imaging procedure have previously been published [12]. The screening group was examined annually, using a multi-slice CT system (16 rows Philips Mx 8000, Philips Medical Systems). Scans were performed supine at full inspiration with a low-dose technique (120 kV and 40 mAs). Two sets of images were then reconstructed: thick (3 mm) and thin (1 mm) slices using soft and hard algorithms (kernel C and D), respectively. Visual assessment was performed on thin slices, kernel D. Two different sets of all scans were created in random order, and each set was evaluated by one of two observers (MW and LT) that were blinded to person identification and scan dates. Interstitial lung abnormalities were registered by both readers as either absent or present. If present, ILA were further categorized as centrilobular, pleural, or paraseptal nodules, ground-glass attenuation, reticulation and/or honeycombing. The interobserver agreement in the detection of ILA was fair to substantial and has previously been published in greater detail [13]. For categorical data such as the different ILA, we used the results of a single observer (the observer who reported abnormal findings most frequently [MW]). For comparison, we repeated our analyses using results of the second observer (LT), which lead to the same conclusions in all analyses, unless specifically stated.

2.3. Registries

Participants were followed up via the Danish Civil Registry system, which contains the vital information of the entire Danish population. Censoring events were emigration (n = 18), reported missing (n = 2), or end of follow-up (December 2016), whichever occurred first. Death causes were acquired from the Danish Cause of Death Registry, which at the time was updated until December 2015. Death causes were classified into five different groups based on ICD10 codes: cardiovascular disease (ICD10 codes I00-I99), respiratory disease (ICD10 codes J00-J99), lung cancer (ICD10 code C34), non-pulmonary malignancies (ICD10 codes C00-C99, excluding C34), and other causes of death (all remaining ICD10 codes).

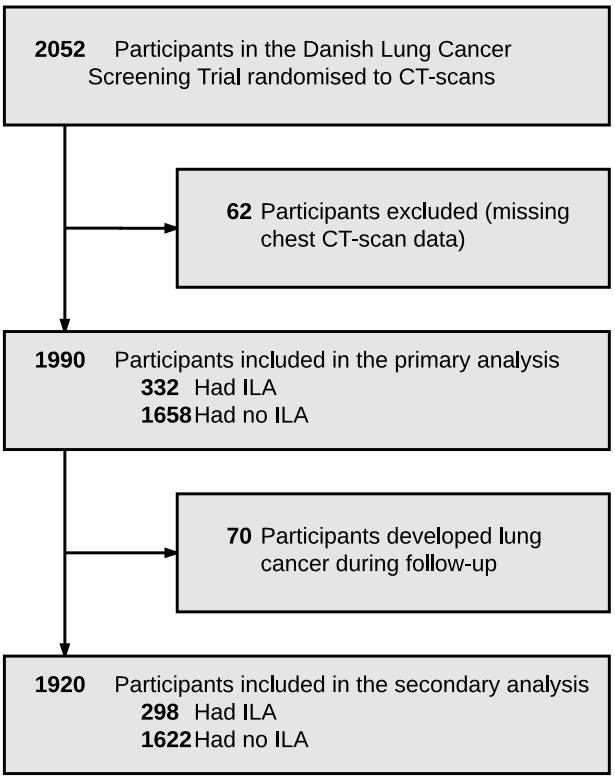

Fig. 1. Generation of the study population for this follow-up study from the intervention arm of the Danish Lung Cancer Screening Trial (DLCST). All participants with chest CT scan data were included in the primary analysis and all participants that remained lung cancer free during follow-up were included in the secondary analysis. ILA: interstitial lung abnormalities.

2.4. Data analysis

Analysis of baseline characteristics and causes of death in the cohort was performed with an unpaired t-test or Fisher's exact test for continuous and categorical variables, respectively.

Survival analysis was performed with Cox regression models adjusting for age, sex, smoking status (active or former), pack-years, BMI, and FEV_1. Continuous covariates were included after checking for linearity in the Cox model. Linearity was not justified for BMI as a continuous variable and it was therefore included as an unordered categorical variable with the categories underweight (BMI < 18.5), normal (BMI 18.5–25) and overweight (BMI > 25). All models were assessed for proportional hazards and no violations of this assumption were found. Biologically plausible interaction terms, such as interaction between sex and FEV_1, were tested for, and no significant interactions were found. To improve adjustment for age, we also performed a Cox regression replacing time-on-study with age as the timescale, which is recommended for epidemiological data where age is expected to be a substantial confounder [14]. We also repeated the Cox regression stratified according to age groups with five-year intervals. Survival analysis was repeated after dividing all ILA into fibrotic (reticulation and honeycombing) or exclusively non-fibrotic (ground glass opacities and nodular pattern) as the rate of radiologic progression has been shown to be dependent on this distinction [4]. The cause of death

Table 1
Baseline characteristics of participants with or without a baseline CT finding of ILA. SD: standard deviation, BMI: body mass index, FEV_1: forced expiratory volume in 1 second, FVC: forced vital capacity.

	All participants			Participants without lung cancer		
	ILA (n = 332)	No ILA (n = 1658)	*P*-value	ILA (n = 298)	No ILA (n = 1622)	*P*-value
Age mean (SD), years	59.7 (5.0)	57.6 (4.7)	< 0.001	59.5 (4.9)	57.6 (4.7)	< 0.001
Female, *n* (%)	136 (41)	742 (45)	0.2	119 (40)	725 (45)	0.1
BMI, mean (SD)	24.9 (4.0)	25.3 (3.8)	0.06	24.8 (3.9)	25.3 (3.8)	0.07
Current/former smokers, *n* (%)	256/76 (77/23)	1243/415 (74/26)	0.4	229/69 (77/23)	1213/409 (75/25)	0.5
Pack-years, mean (SD)	37.5 (13.4)	36.2 (13.4)	0.1	37.5 (13.6)	36.0 (13.4)	0.08
FEV_1 l, mean (SD)	2.75 (0.76)	2.91 (0.75)	< 0.001	2.80 (0.76)	2.92 (0.75)	0.01
FEV_1% predicted, mean (SD)	87.9 (18.6)	92.4 (16.3)	< 0.001	89.2 (18.1)	92.6 (16.2)	0.002
FVC l, mean (SD)	4.03 (1.0)	4.13 (0.99)	0.1	4.08 (1.00)	4.14 (0.99)	0.3
FVC % predicted, mean (SD)	99.5 (17.7)	101.7 (15.3)	0.04	100.3 (17.3)	101.8 (15.2)	0.2
FEV_1/FVC, mean (SD)	0.68 (0.09)	0.71 (0.08)	< 0.001	0.69 (0.09)	0.71 (0.08)	< 0.001
Follow-up time median, years (IQR)	11.22 (10.77–11.75)	11.29 (11.03–11.75)	< 0.001	11.24 (10.93–11.73)	11.30 (11.04–11.75)	0.03

analysis was performed with a competing risk multiple Cox regression with all other death causes (including unknown death causes) treated as censoring events.

All *P*-values are two-sided and a *P*-value < 0.05 was considered significant. All statistical analyses were performed with the statistical package R (version 3.3.3).

3. Results

3.1. Prevalence of ILA

Interstitial lung abnormalities were found in the baseline scans of 332 participants (16.7%). Participants with ILA were generally older, had more airway obstruction and tended to have been exposed to more pack-years, compared to participants without ILA (Table 1, Fig. 2). When limiting the analysis to participants who remained lung cancer free during follow-up, ILA were found in 298 participants (15.5%) (Table 1).

3.2. Association of ILA with mortality

In multiple Cox regression models, a finding of ILA at baseline was associated with an increase in all-cause mortality (HR: 2.0, 95% CI: 1.4–2.7, $P < 0.001$) over a period of up to twelve years of follow-up (Table 2). This increase in mortality was still significant when excluding participants that developed lung cancer during follow-up (HR: 1.6, 95% CI: 1.1–2.4, $P = 0.007$) (Table 2).

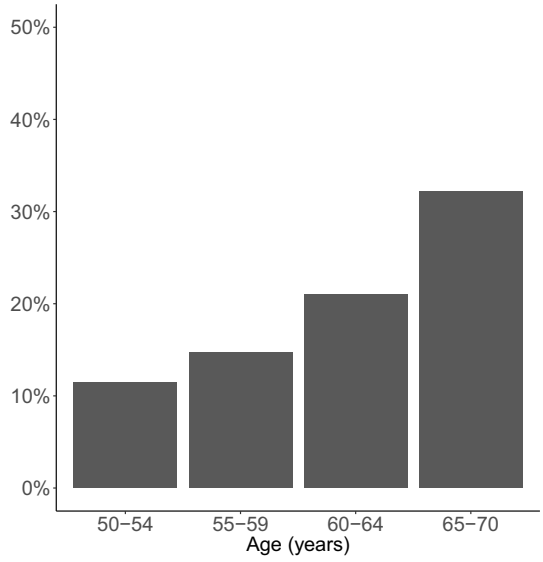

Fig. 2. Proportion of participants with a finding of ILA at baseline divided into four age groups. The plot is based on all participants, including those who developed lung cancer during follow-up.

3.3. Age and ILA

Older participants in our cohort were more likely to have ILA (Table 1, Fig. 2). However, repeating the Cox regression analysis with age as timescale, rather than time-on-study, did not alter the effect size or significance in either the full cohort (HR: 2.0, 95% CI: 1.5–2.7, $P < 0.001$) or in lung cancer-free participants (HR: 1.7, 95% CI: 1.2–2.4, $P = 0.006$) (Fig. 3).

After dividing participants into age groups in 5-year intervals based on age at the time of CT scan, the association of ILA with mortality remained significant in the two largest age groups, containing participants aged 55–60 years (HR: 2.3, 95% CI: 1.2–4.1, $P = 0.003$) and 60–65 years (HR: 2.1, 95% CI: 1.2–3.5, $P = 0.005$) in multiple Cox regression analyses. The other age groups contained fewer participants and we found no significant association between ILA and mortality within these groups.

3.4. ILA morphology and mortality

To determine if the increased mortality was caused by a specific radiological finding, we investigated the different ILA morphologies (ground-glass opacities, nodular pattern, reticulation, and honeycombing) separately. All investigated findings were associated with mortality, both in the entire cohort and when limiting the analysis to participants that remained lung cancer-free during follow-up (Table 2). The most detrimental finding was honeycombing, both in the full cohort (HR: 6.7, 95% CI: 2.9–15.4, $P < 0.001$) and in lung cancer-free participants (HR: 4.2, 95% CI: 1.0–17.2, $P = 0.04$) (Table 2).

When dividing the findings into fibrotic ILA (reticulation and honeycombing) and exclusively non-fibrotic ILA (nodular pattern and ground-glass opacities), multiple Cox regression showed no difference in survival between the two groups ($P = 0.8$) (Fig. 4).

3.5. Causes of death

To further elucidate the increased mortality associated with ILA, we investigated the registered cause of death for all participants. ILA findings were associated with increased deaths from lung cancer (HR: 3.2, 95% CI: 1.7–6.2, $P < 0.001$) and non-pulmonary malignancies (HR: 2.1, 95% CI: 1.1–4.0, $P = 0.02$) in competing risk Cox regression models (Table 3). Deaths attributable to cardiovascular and respiratory disease in this cohort seemed independent of ILA (Table 3). Repeating the analyses using scores from a different reader (LT) resulted in the same conclusion for lung cancer, but did not show an association

Table 2
Prevalence and adjusted hazard ratio of mortality for different ILA in the entire cohort or lung cancer-free participants, respectively. Multiple Cox regression models were adjusted for age, sex, smoking status, pack-years, FEV_1, and BMI. There can be multiple types of ILA in one scan. HR: hazard ratio, CI: confidence interval, BMI: body mass index, FEV_1: forced expiratory volume in 1 second.

	All participants			Participants without lung cancer		
	n (%)	HR (95% CI)	*P*-value	*n* (%)	HR (95% CI)	*P*-value
Any ILA	332 (16.7)	2.0 (1.4–2.7)	< 0.001	298 (15.5)	1.6 (1.1–2.4)	0.007
Ground glass	115 (5.8)	2.3 (1.5–3.4)	< 0.001	99 (5.2)	1.8 (1.1–3.0)	0.03
Nodular pattern	155 (7.8)	2.2 (1.5–3.2)	< 0.001	141 (7.3)	2.1 (1.4–3.3)	< 0.001
Reticulation	162 (8.1)	1.8 (1.2–2.6)	0.004	144 (7.5)	1.6 (1.0–2.6)	0.03
Honeycombing	12 (0.6)	6.7 (2.9–15.4)	< 0.001	8 (0.4)	4.2 (1.0–17.2)	0.04

between ILA and non-pulmonary malignancies (HR: 1.1, 95% CI: 0.5–2.2, $P = 0.87$).

4. Discussion

Interstitial lung abnormalities were a common finding in the Danish Lung Cancer Screening Trial population and were associated with increased mortality, regardless of the underlying morphological phenotype. A finding of ILA in this group of relatively healthy smokers was a risk factor for death from lung cancer and possibly non-pulmonary malignancies.

The prevalence of ILA (16.7%) in this cohort was similar to previous reports of lung cancer screening populations, which report a prevalence of 9.7%–22.8% [3,4]. Possible explanations for this high prevalence include the use of full chest CT scans and the participants' high age and tobacco exposure. We did not classify any findings as indeterminate, but included all ILA in our analysis, regardless of the intensity and overall radiological pattern, which may have contributed to the high prevalence [3,4,7,9].

Interestingly, a finding of ILA was not dependent on smoking status at baseline, although there was a non-significant trend towards more frequent ILA in participants with more pack-years. This is in contrast to previous findings from lung cancer screening and general population cohorts [4,6,9], but similar to some cohorts of patients with significant smoking exposure and chronic obstructive pulmonary disease (COPD) [9]. A possible explanation for this discrepancy could be a non-linear relationship between smoking and ILA, where additional exposure beyond 20 pack-years (the inclusion criteria for our cohort) has less impact on the presence of ILA compared to less extreme exposure.

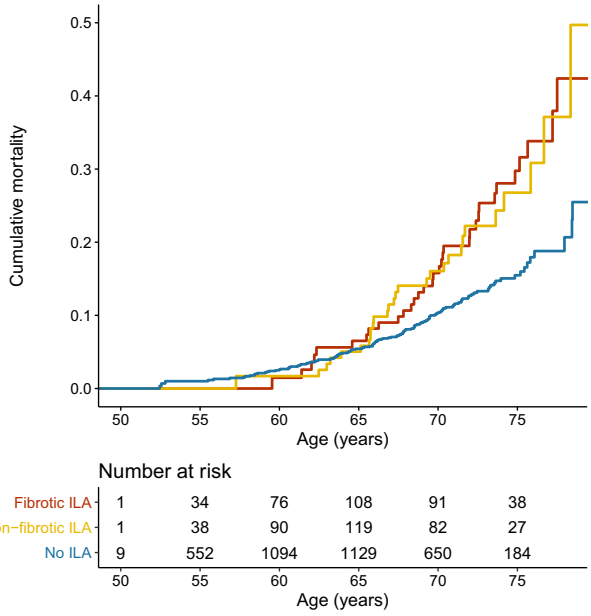

Fig. 4. Cumulative all-cause mortality in participants stratified according to ILA at baseline. Participants with any type of fibrotic ILA (reticulation and honeycombing) were compared to exclusively non-fibrotic ILA (nodular pattern or ground-glass opacities) or no ILA. The mortality curves use age as the timescale and represent the full cohort with all participants. The risk set varies because the data is both left truncated and right censored. For curves with time-on-study as timescale, see the online supplemental data.

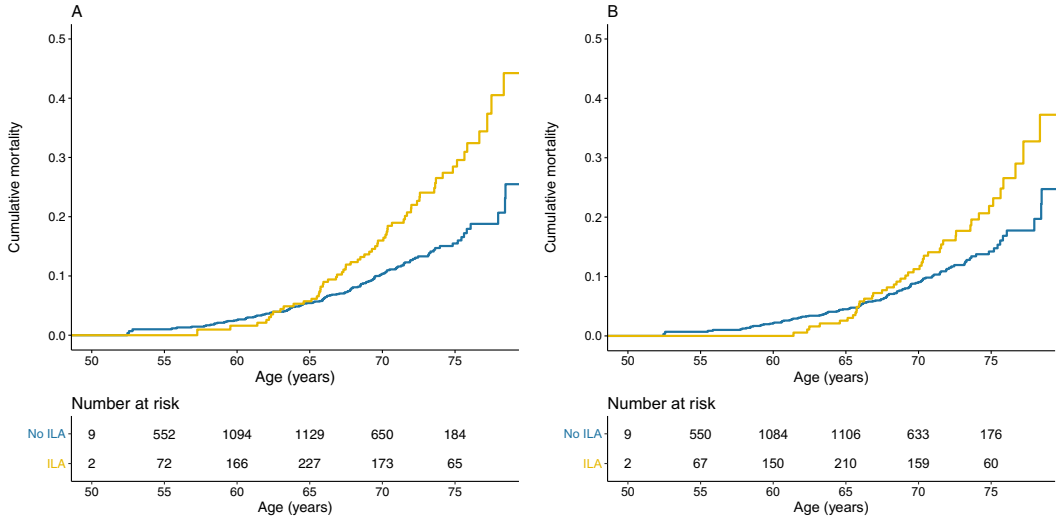

Fig. 3. Cumulative all-cause mortality in participants stratified according to ILA at baseline. The mortality curves use age as a timescale and represent the full cohort with all participants (*A*) or the participants who remained lung cancer free during follow-up (*B*). The risk set varies because the data is both left truncated and right censored. For curves with time-on-study as timescale, see the online supplemental data.

Table 3
Number of specified causes of death in each group until December 2015 in participants with or without ILA, respectively. The full cohort was used in this analysis, including participants that developed lung cancer during follow-up. Hazard ratio (HR) was calculated using multiple Cox regression models, with all other death causes (including unknown death causes) as competing risk. The Cox models were controlled for age, sex, smoking status, pack years, BMI, and FEV_1. The analyses are based on CT findings of reader MW. CI: confidence interval, BMI: body mass index, FEV_1: forced expiratory volume in 1 second.

Death cause	ILA (n = 332)	No ILA (n = 1658)	HR (95% CI)	P-value
Cardiovascular disease	7	15	1.8 (0.7–4.7)	0.20
Respiratory disease	5	9	2.0 (0.7–6.2)	0.22
Lung cancer	17	23	3.2 (1.7–6.2)	< 0.001
Non-pulmonary malignancies	15	31	2.1 (1.1–4.0)	0.02
Other causes	8	29	1.3 (0.6–2.9)	0.50
Total	**52**	**107**		

We show for the first time, that several ILA morphologies are associated with mortality. This suggests that no single radiological finding and thus, probably no single disease entity, is exclusively responsible for the increased mortality associated with ILA. The rare finding of honeycombing was associated with the greatest increase in mortality, which can be explained by honeycombing representing end-stage fibrotic lung disease. The strong association with the exclusively non-fibrotic findings (i.e. ground-glass opacities and nodular patterns in the absence of any fibrosis) over a 12-year follow-up period was surprising because these have been shown to be more stable compared with fibrotic ILA [4]. One possible explanation for this finding is that non-fibrotic ILA represent premalignant changes, explaining the increased incidence of lung cancer, or pro-inflammatory conditions impacting mortality due to other cancers. However, it is also possible that ILA is merely a surrogate marker, rather than a contributor to the poor prognosis.

We found a clear relationship between age and the presence of ILA, requiring rigorous statistical adjustment to disprove that the increased mortality in participants with ILA is simply due to their higher age alone. Using age as a timescale in survival models has been shown to be superior in adjusting for the confounding effects of age in epidemiologic studies [14]. However, even after this adjustment, ILA were associated with mortality in our cohort. Further stratification into 5-year age groups did not alter the association either. The significance of ILA, even after rigorous adjustment for age as a confounding variable, suggests that the association with mortality can be only partially explained by the older age of the participants with ILA.

We found ILA to be associated with death from both lung cancer and non-pulmonary malignancies, which is consistent with previous results showing that smokers with lung cancer often have histopathological fibrosis in their lungs and that lung cancer is strongly associated with ILA [15,16]. Our results show that ILA findings during lung cancer screening should not be ignored, as they are a risk factor for later death from clinical lung cancer. Thus, an ILA finding should be considered as a selection criterion in a targeted lung cancer screening program. However, the exclusion of all participants that developed lung cancer did not remove the association between ILA and mortality. We therefore suggest that the increased mortality in this population is not due to the increase in lung cancer alone. Another contributing factor was the less pronounced association between ILA and death from non-pulmonary malignancies. A comparable association between radiological lung findings and non-pulmonary malignancies has been shown for emphysema [17]. This association could be due to shared genetic or environmental risk factors between ILA and non-pulmonary malignancies including extra-pulmonary effects of smoking. Previously reported increased odds of death due to respiratory causes, including lung fibrosis, in a general population with ILA could not be replicated in this lung cancer screening population, presumably due to the low number of respiratory deaths including deaths due to interstitial lung disease [9]. The low frequency of respiratory deaths (other than lung cancer) in this cohort of heavy smokers was surprising but could be explained by respiratory disease being considered a contributing cause, rather than the direct cause of death in some participants. Considering death causes alone may underestimate the prevalence of respiratory disease in smokers with ILA, which underscores the need for further research of the morbidity related to ILA in this group, including the development of clinically manifest interstitial lung diseases.

4.1. Limitations

Our study has several limitations that need to be considered.

We excluded 62 participants without CT scan data. These were participants who died or dropped out within the first year after inclusion.

Using results from only one reader is a limitation, which we tried to address in the following ways. Repeating analyses with the findings from a second reader yielded comparable results in all instances except one. In contrast to previous reports, we did not code any findings as 'indeterminate', but limited the analysis to a simple dichotomous variable of ILA or no ILA. This potentially weakened our conclusions by including less severe findings in the 'exposed' group. However, any cut-off between different grades of severity would be arbitrary and not easily transferred to clinical practice, which could make it difficult to interpret. In addition, we relied on qualitative descriptors of ILA in contrast to quantitative measures. This reduces the repeatability of our findings and reduces the data quality. However, our approach is similar to the use of imaging in clinical practice today and several comparable studies [3,5,9].

Data on the participant's subsequent clinical diagnosis and treatment for interstitial lung disease were not available for analysis. It could be expected that treatment affects the association between ILA and mortality and this information should ideally be included in the statistical analysis.

Low diffusion capacity is associated with increased mortality in interstitial lung disease and would have been relevant to include in the analysis, but data on diffusion capacity are not available in the DLCST [18]. Consequently, we are unable to assess the effect of the ILA changes that is mediated through low diffusion.

The cause of death data was based on data from death certificates with all the well-known uncertainties and inaccuracies of this approach. However, cancer diagnoses were histologically verified.

Our analysis was based on findings from low-dose CT scans, rather than high resolution CT (HRCT), which is the standard imaging test in the diagnosis of interstitial lung disease. Although low-dose CT can give false positive ILA findings [5], this limitation is inherent to lung cancer screening, which is performed by low-dose CT to reduce radiation exposure. Consequently, our results demonstrate the ILA findings that would be expected from lung cancer screening.

5. Conclusion

Interstitial lung abnormalities were common in the Danish Lung Cancer Screening Trial population and were associated with increased mortality, regardless of the interstitial morphological phenotype. The increased mortality could be partly explained by increased age and death due to both lung cancer and non-pulmonary malignancies. Our findings have important implications for future lung cancer screening programs.

Contributorship

NH collected registry data, analysed data and wrote the manuscript.

MMWW and LHT analysed CT scans. SBS and TW conceived the idea and edited the manuscript. AD, JHP, ZS and HA performed the original study, collected data, and critically revised the manuscript. All authors contributed to the intellectual development of the work, revised and approved the final manuscript.

Conflicts of interest

NH has received unrestricted research grants from Roche a/s, Herlev and Gentofte hospital, P.A. Messerchmidt og Hustrus fond, and Direktør Kurt Bønnelycke og hustru fru Grethe Bønnelyckes Fond. The authors declare no other relationship with any companies whose products or services may be related to the subject matter of the article.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.rmed.2018.02.001.

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