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Interstitial lung abnormalities are associated with increased mortality in smokers

Nils Hoyer[a,*], Mathilde M.W. Wille[b], Laura H. Thomsen[c], Torgny Wilcke[a], Asger Dirksen[a], Jesper H. Pedersen[d], Zaigham Saghir[a], Haseem Ashraf[a,e], Saher B. Shaker[a]

[a] Department of Respiratory Medicine, Herlev and Gentofte Hospital, Copenhagen, Denmark
[b] Department of Radiology, Bispebjerg Hospital, Copenhagen, Denmark
[c] Department of Respiratory Medicine, Amager and Hvidovre Hospital, Copenhagen, Denmark
[d] Department of Cardiothoracic Surgery RT, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark
[e] Department of Radiology, Akershus University Hospital, Loerenskog, Norway

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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.

* Corresponding author. Department of Respiratory Medicine, Herlev and Gentofte Hospital, Kildegårdsvej 28, 2900 Hellerup, Denmark.
E-mail address: nils.hoyer.01@regionh.dk (N. Hoyer).

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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).

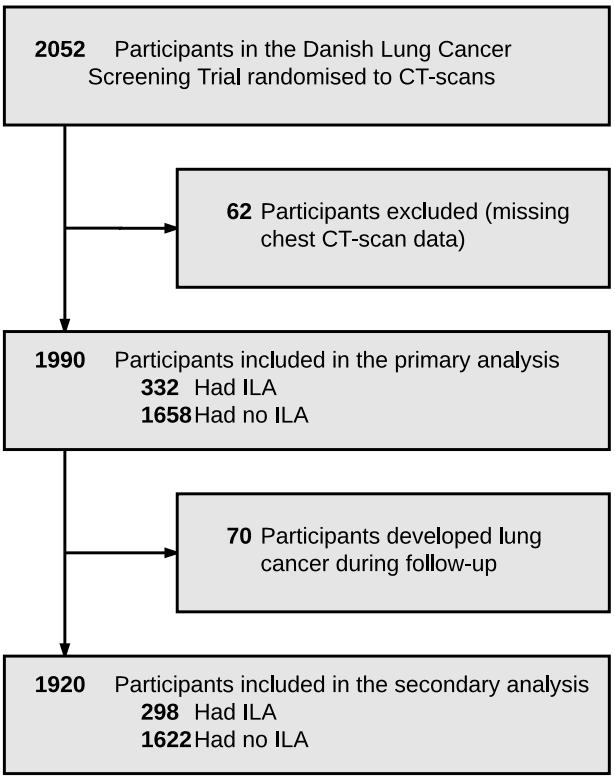

Fig. 1. Generation of the study population for this follow-up study from the intervention arm of the Danish Lung Cancer Screening Trial (DLCST). All participants with chest CT scan data were included in the primary analysis and all participants that remained lung cancer free during follow-up were included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