The associations of interstitial lung abnormalities with cancer diagnoses and mortality

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Interstitial lung abnormalities are associated with an increased hazard of lung cancer diagnosis and lung cancer mortality in a general population cohort. Cancers other than lung cancer were not associated with interstitial lung abnormalities. https://bit.ly/3hWdc6m

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ABSTRACT An increased incidence of lung cancer is well known among patients with idiopathic pulmonary fibrosis. It is not known whether interstitial lung abnormalities, *i.e.* early fibrotic changes of the lung, are a risk factor for lung cancer in the general population.

The study's objective was to assess whether interstitial lung abnormalities were associated with diagnoses of, and mortality from, lung cancer and other cancers. Data from the AGES-Reykjavik study, a cohort of 5764 older Icelandic adults, were used. Outcome data were ascertained from electronic medical records. Gray's tests, Cox proportional hazards models and proportional subdistribution hazards models were used to analyse associations of interstitial lung abnormalities with lung cancer diagnoses and lung cancer mortality as well as diagnoses and mortality from all cancers.

There was a greater cumulative incidence of lung cancer diagnoses (p<0.001) and lung cancer mortality (p<0.001) in participants with interstitial lung abnormalities than in others. Interstitial lung abnormalities were associated with an increased hazard of lung cancer diagnosis (hazard ratio 2.77) and lung cancer mortality (hazard ratio 2.89) in adjusted Cox models. Associations of interstitial lung abnormalities with all cancers were found in models including lung cancers but not in models excluding lung cancers.

People with interstitial lung abnormalities are at increased risk of lung cancer and lung cancer mortality, but not of other cancers. This implies that an association between fibrotic and neoplastic diseases of the lung exists from the early stages of lung fibrosis and suggests that interstitial lung abnormalities could be considered as a risk factor in lung cancer screening efforts.

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Introduction

Interstitial lung abnormalities (ILA) are commonly defined as abnormalities noted on chest computed tomography (CT) scans that are similar in appearance to those noted in patients with interstitial lung disease but occurring in a person without a known diagnosis of interstitial lung disease [1]. There is evidence to suggest that some research participants with ILA may share a common syndrome noted in patients with idiopathic pulmonary fibrosis (IPF) that includes the development of a restrictive lung deficit [1], accelerated lung function decline [2], imaging progression [2, 3], shared genetic determinants [4, 5], poorer subjective health and physical function, and increased rates of mortality [6–8]. ILA have been further categorised into specific subtypes and imaging patterns [1, 3]. Associations with restrictive lung deficits, genetic polymorphisms, imaging progression and mortality have been found to vary between these subtypes and patterns [1, 3, 9].

A number of studies have demonstrated an increased incidence of lung cancer among IPF patients compared with the general population, even when adjusted for confounders such as cigarette smoking [10, 11]. The development of lung cancer in IPF patients has been shown to severely impair their survival [12]. While ILA have been associated with increased prevalence of, and mortality from, lung cancer in cohorts of smokers intended for lung cancer screening [13–16], there is less known about these risks in the general population. In addition, data are scarce regarding whether there is an increased risk of non-pulmonary malignancies among people with ILA.

Thus, the objectives of this study were to explore the associations of ILA with diagnoses of both lung cancer and other cancers and to assess whether ILA were associated with increased mortality from lung cancer and other malignancies.

Methods

Data acquisition and materials

The Age, Gene/Environment Susceptibility-Reykjavik (AGES-Reykjavik) study is a longitudinal birth cohort study, derived from the previous Reykjavik study, in which older individuals were recruited between 2002 and 2006 in an effort to identify the causal factors of diseases and disabilities associated with ageing. Additional details on the study design have been previously published [17].

CT imaging of the thorax was characterised for the presence of ILA in 5320 out of 5764 AGES-Reykjavik participants (92%) by up to three readers, as previously described [1]. ILA were defined as nondependent ground-glass or reticular abnormalities, diffuse centrilobular nodularity, non-emphysematous cysts, honeycombing and traction bronchiectasis that affected >5% of any lung zone [1]. Participants who had focal or unilateral ground-glass attenuation, focal or unilateral reticulation and patchy ground-glass abnormalities present in <5% of any lung zone were regarded as having indeterminate changes [1]. Images from participants with ILA were further classified by the presence of the definite fibrosis imaging pattern, defined as pulmonary parenchymal architectural distortion consistent with a fibrotic lung disease [3].

Data on cancer diagnoses were available in 5270 (99%) of the 5320 AGES-Reykjavik participants previously characterised for ILA.

Participants were followed from their entry into the study (between 2002 and 2006) until their first diagnosis of cancer or until the end of observation (August 31, 2016). Information regarding cancer diagnoses was ascertained from electronic medical records from Landspitali University Hospital, Iceland's largest, and only tertiary care, hospital. Participants' hospital visits with a registered International Classification of Diseases, Tenth Revision (ICD-10) diagnosis ranging from C00 to C97 were defined as cancer diagnoses, with the date of the first such visit defined as the date of first diagnosis. Lung cancer diagnoses were likewise defined from hospital visits with a registered ICD-10 diagnosis starting with C34. Information on mortality and causes of death was obtained from the Icelandic Directorate of Health, with follow-up from study entry until the end of August 2016. Mortality from cancer was defined as having the cause of death registered as C00–C97, coded according to the ICD-10, while mortality from lung cancer was defined as having C34 as the registered cause of death.

Statistical analyses

Comparable to previous studies [4, 6], participants indeterminate for ILA were excluded from analyses of the associations between ILA, cancer diagnoses and cancer-associated mortality. The cumulative incidences of lung cancer diagnoses and diagnoses of other cancers among participants with and without ILA were calculated, with the risk of mortality regarded as a competing risk. Gray's tests were used to assess for differences in these cumulative incidences. The cumulative incidences of mortality from lung cancer, mortality from non-pulmonary cancers and mortality from other causes were calculated and compared between participants with and without ILA using Gray's tests with all risks regarded as competing.

Cox proportional hazards models were used to quantify the associations of ILA and several outcomes: lung cancer diagnoses, diagnoses of all cancers, mortality from lung cancers and mortality from all cancers. The proportional hazards assumption was tested and graphically verified for all models. The covariates included in all adjusted models were age, sex, pack-years of smoking and smoking at the beginning of the study. In addition, models analysing the associations of ILA with diagnoses of all cancers and mortality from all cancers were constructed in which lung cancer diagnoses and lung cancer mortality were excluded from the outcomes. Identical Cox proportional hazards models were created in which participants with ILA were compared with both participants indeterminate for ILA and participants without ILA. Results from these models are shown in the supplementary material.

Proportional subdistribution hazards models [18] were created to verify results from Cox models using regression methods accounting for competing risks. To assess whether lung cancer outcomes differed depending on the presence of the definite fibrosis pattern, adjusted and unadjusted Cox proportional hazards models were created. In these models, the associations of lung cancer diagnoses and mortality from lung cancer were assessed, comparing participants with ILA and definite fibrosis or ILA without definite fibrosis to participants without ILA.

Statistical analyses were done using R, version 3.5.2 (R Project for Statistical Computing, Vienna).

Results

Participants' characteristics

Demographic variables and the incidence of cancer diagnoses in participants stratified by ILA status are included in table 1. Comparable to previous reports [8], participants with ILA were on average older, more likely to be male and more likely to be exposed to tobacco smoke than participants without ILA.

ILA and cancer diagnoses

Subsequent to study entry, participants with ILA were more likely to have received a diagnosis of cancer overall, and lung cancer specifically, than participants without ILA (table 1).

The cumulative incidences of lung cancer diagnoses and other cancer diagnoses are displayed in figure 1. There was a greater cumulative incidence of lung cancer diagnoses among participants with ILA than

TABLE 1 Baseline participant characteristics

	No ILA	Indeterminate for ILA	ILA
Participants n	3183	1712	375
Age years	76.0±5.4	77.4±5.7	77.8±5.6
Women	1887 (59)	953 (56)	170 (45)
BMI kg·m^{-2}	27.2±4.4	26.8±4.4	27.0±4.6
History of smoking	1732 (54)	1013 (59)	269 (72)
Median pack-years (IQR)	0 (0–16)	2.5 (0–23)	11 (0–28)
Current smoker	368 (12)	203 (12)	68 (18)
Days of follow-up to all-cause mortality	3675±1228	3396±1347	2981±1433
Imaging patterns			
Without fibrosis			246 (66)
Definite fibrosis			129 (34)
Participants diagnosed with cancer before beginning of study			
Overall	194 (6.1)	132 (7.7)	32 (8.5)
Participants diagnosed with cancer after beginning of study			
Overall	668 (21)	383 (22)	97 (26)
Lung cancer (C34)	77 (2.4)	58 (3.4)	27 (7.2)
Gastrointestinal cancer (C15–C26)	176 (5.5)	86 (5.0)	20 (5.3)
Skin cancers (C43–C44)	45 (1.4)	30 (1.8)	4 (1.1)
Cancers of breasts and female genitalia (C50–C58)	108 (3.4)	44 (2.6)	8 (2.1)
Cancers of male genitalia (C60–C63)	124 (3.9)	71 (4.1)	20 (5.3)
Urinary tract cancers (C64–C68)	81 (2.5)	49 (2.9)	11 (2.9)
Haematologic malignancies (C81–C96)	57 (1.8)	34 (2.0)	9 (2.4)
Mortality due to cancer during study follow-up			
Cancer overall	388 (12)	232 (14)	63 (17)
Lung cancer (C34)	65 (2.0)	61 (3.6)	25 (6.7)

Data are presented as mean±SD or n (%), unless otherwise stated. ILA: interstitial lung abnormalities; BMI: body mass index; IQR: interquartile range.

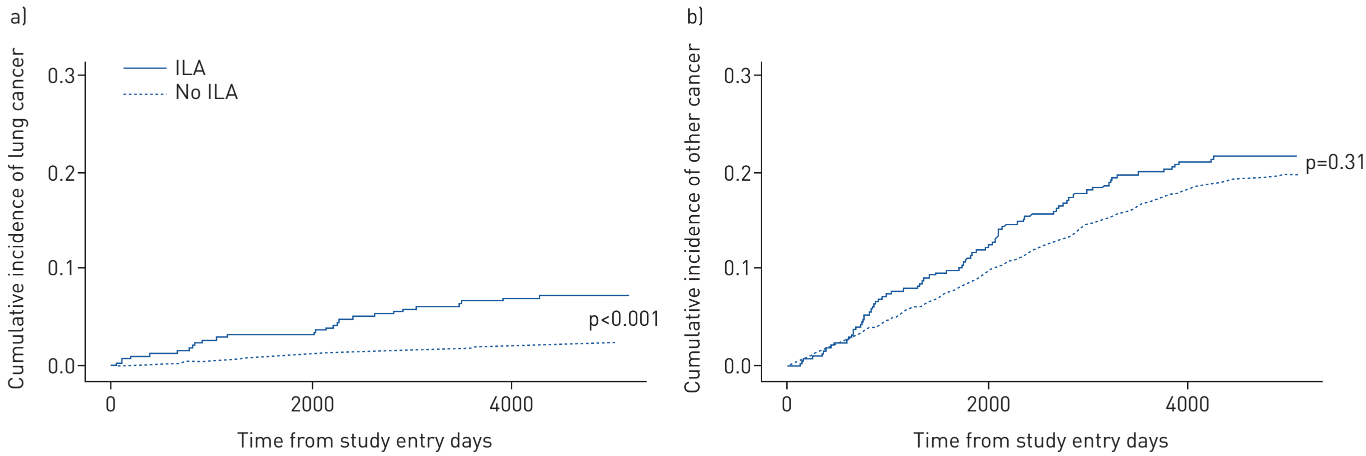

FIGURE 1 Cumulative incidence of cancer diagnoses among participants with and without interstitial lung abnormalities (ILA). p-values are for differences in the cumulative incidence of cancer diagnoses between participants with ILA and participants without ILA for a) lung cancer and b) other cancers using Gray's tests.

among participants without ILA ($p<0.001$). There were no significant differences in the cumulative incidences of other cancer diagnoses between participants with and without ILA (figure 1).

In Cox proportional hazards models, participants with ILA were at increased risk of lung cancer diagnosis than those without ILA, both in an unadjusted model (hazard ratio (HR) 3.76, 95% CI 2.42–5.84, $p=3.59\times10^{-9}$) and in a model adjusting for age, sex, pack-years of smoking and smoking at the beginning of the study (HR 2.77, 95% CI 1.76–4.36, $p=1.08\times10^{-5}$) (table 2). In adjusted models, the increase in risk of lung cancer diagnosis was statistically significant for both participants with the definite fibrosis imaging pattern (HR=3.95, 95% CI=2.07–7.57, $p=3.32\times10^{-5}$) and without it (HR=2.26, 95% CI=1.29–3.96, $p=0.004$), although participants with fibrosis were at greater risk (table 3). Participants with ILA were at an increased risk of diagnosis of cancer overall in adjusted models (HR 1.35, 95% CI 1.09–1.68, $p=0.006$). In contrast, the increase in risk of a diagnosis of all cancers excluding lung cancers was not statistically significant among participants with ILA (HR 1.24, 95% CI 0.98–1.57, $p=0.07$) (table 2).

ILA and mortality from cancer

The cumulative incidences of mortality from lung cancer and mortality from cancers other than lung cancer are displayed in figure 2. There was greater mortality from lung cancer among participants with ILA than without ILA ($p<0.001$), as well as greater mortality from causes other than cancer. However, mortality from cancers other than lung cancer was not increased among participants with ILA (figure 2).

In unadjusted Cox proportional hazards models, participants with ILA were at increased risk of death from all cancers (HR 1.81, 95% CI 1.39–2.37, $p=1.23\times10^{-5}$) and from lung cancer specifically (HR 4.19, 95% CI 2.64–6.66, $p=1.27\times10^{-9}$) compared to those without ILA. In models adjusting for age, sex,

TABLE 2 Associations of interstitial lung abnormalities (ILA) with cancer diagnoses

Model	HR (95% CI)	p-value
Lung cancer diagnoses		
Unadjusted	3.76 (2.42–5.84)	3.59×10^{-9}
Adjusted	2.77 (1.76–4.36)	1.08×10^{-5}
Cancer diagnoses of all causes		
Unadjusted	1.57 (1.27–1.95)	3.07×10^{-5}
Adjusted	1.35 (1.09–1.68)	0.006
Cancer diagnoses of all causes excluding lung cancer		
Unadjusted	1.39 (1.11–1.76)	0.005
Adjusted	1.24 (0.98–1.57)	0.07

All models are Cox proportional hazards models of the association of ILA with the specified cancer diagnoses. Adjusted models are adjusted for age, sex, pack-years and smoking at entry. HR: cause-specific hazard ratio.

TABLE 3 Associations of imaging patterns with lung cancer diagnoses and mortality

Model	HR (95% CI)	p-value
Definite fibrosis		
Lung cancer diagnoses		
Unadjusted	5.49 (2.91–10.4)	1.56×10^{-7}
Adjusted	3.95 (2.07–7.57)	3.32×10^{-5}
Mortality from lung cancer		
Unadjusted	8.86 (4.94–15.9)	2.37×10^{-13}
Adjusted	5.98 (3.29–10.9)	4.17×10^{-9}
Without fibrosis		
Lung cancer diagnoses		
Unadjusted	3.10 (1.81–5.32)	3.90×10^{-5}
Adjusted	2.26 (1.29–3.96)	0.004
Mortality from lung cancer		
Unadjusted	2.53 (1.33–4.79)	0.005
Adjusted	1.68 (0.86–3.29)	0.13

All models are Cox proportional hazards models of the association of the specified pattern of interstitial lung abnormalities (ILA) with diagnoses of, or mortality from, lung cancer. All comparisons are made with participants without ILA. Adjusted models are adjusted for age, sex, pack-years and smoking at entry. HR: cause-specific hazard ratio.

pack-years of smoking and smoking at the beginning of the study, the same was true for death from cancer overall (HR 1.47, 95% CI 1.12–1.94, p=0.005) and from lung cancer (HR 2.89, 95% CI 1.80–4.66, $p=1.26\times10^{-5}$). However, the risk of death from all cancers excluding lung cancer was not statistically significantly increased among those with ILA (HR 1.15, 95% CI 0.82–1.61, p=0.43) (table 4). Participants with definite fibrosis were, in adjusted models, at increased risk of death from lung cancer (HR 5.98, 95% CI 3.29–10.9, $p=4.17\times10^{-9}$). This increase was not statistically significant for participants with ILA without definite fibrosis (HR 1.68, 95% CI 0.86–3.29, p=0.13) (table 3).

In proportional subdistribution hazards models adjusted for covariates, ILA was also found to be associated with an increased risk of lung cancer diagnosis (HR 2.63, 95% CI 1.58–4.38, $p=1.9\times10^{-4}$) and mortality from lung cancer (HR 2.55, 95% CI 1.56–4.18, $p=2.1\times10^{-4}$).

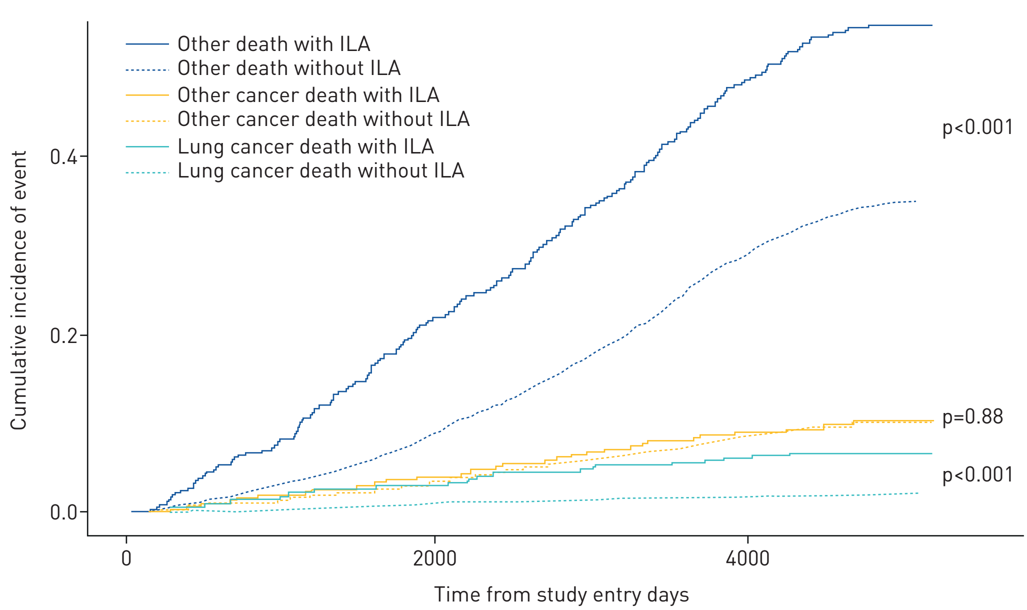

FIGURE 2 Cumulative incidence of cancer mortality among participants with and without interstitial lung abnormalities (ILA). p-values are for differences in the cumulative incidence of mortality due to the specified cause between participants with ILA and participants without ILA using Gray's tests.

TABLE 4 Associations of interstitial lung abnormalities (ILA) with mortality from cancer

Model	HR (95% CI)	p-value
Mortality from lung cancer		
Unadjusted	4.19 (2.64–6.66)	1.27×10^{-9}
Adjusted	2.89 (1.80–4.66)	1.26×10^{-5}
Mortality from all cancers		
Unadjusted	1.81 (1.39–2.37)	1.23×10^{-5}
Adjusted	1.47 (1.12–1.94)	0.005
Mortality from all cancers excluding lung cancer		
Unadjusted	1.32 (0.94–1.85)	0.10
Adjusted	1.15 (0.82–1.61)	0.43

All models are Cox proportional hazards models of the association of ILA with mortality from the specified cancers. Adjusted models are adjusted for age, sex, pack-years and smoking at entry. HR: cause-specific hazard ratio.

Discussion

These results demonstrate that AGES-Reykjavik participants with ILA are at an increased risk of both lung cancer diagnosis and mortality from lung cancer. These associations between ILA, lung cancer and lung cancer-associated mortality were consistent between Cox proportional hazards models and methods accounting for the competing risks of other cancer diagnoses or other causes of mortality. Associations varied with ILA patterns; participants with the definite fibrosis pattern were at greater risk of lung cancer diagnosis than participants without definite fibrosis, and an increase in lung cancer-associated mortality was only found among participants with definite fibrosis. The associations of ILA, which in some cases may represent early fibrotic changes of the lung [19], with pulmonary malignancies are in concordance with the well-established increase in risk of lung cancer among patients with more advanced pulmonary fibrosis such as IPF [10, 11]. These results also support previous findings from lung cancer screening studies of smokers that demonstrate an increased prevalence of ILA among patients with lung cancer [14, 15], as well as increased mortality from lung cancer among participants with ILA [13, 15]. However, associations of ILA with lung cancer diagnoses and lung cancer mortality have not been reported in a population-based cohort.

The mechanisms underlying these associations are yet to be clarified. It is possible that a common pathobiological process exists for fibrotic lung disease and lung cancer. Several studies have explored this possibility with regards to lung cancer and IPF [20–22]. Among similarities noted in the pathogenesis of these diseases are genetic alterations [22–25], epigenetic similarities including in DNA methylation and altered mRNA expression profiles [20, 24, 26], altered cell-to-cell communication, abnormalities in intracellular signalling pathways and overexpression of several signalling molecules [21, 24, 27, 28]. Besides a common biological pathway, it is possible that the results could be explained by a common, unmeasured risk factor *via* residual confounding. However, the mechanisms underlying these results cannot be determined from the cohort data shown here and thus remain a topic of research.

The results oppose the suggestion that participants with ILA are at an increased risk of diagnoses of and mortality from cancers other than lung cancers. While there were small associations between ILA and these outcomes, they did not reach statistical significance when lung cancer diagnoses were excluded. This is supported by the lack of difference in the cumulative incidence of non-pulmonary cancer diagnoses and mortality from non-pulmonary cancers between participants with and without ILA (figures 1 and 2).

The study has several limitations. Cancer diagnoses were obtained from medical records from the National Hospital of Iceland. The outcome data regarding both cancer diagnoses and mortality are separately registered health record data, meaning that the quality of the data is dependent on the quality of clinicians' diagnoses and clinical registration. Among other limitations is the possibility that unknown confounding factors were not adjusted for. This is especially a concern in analyses regarding diagnoses of all cancers because various cancers have different risk factors that were not all adjusted for in these analyses. The association of ILA with mortality from lung cancer was dependent on the presence of the definite fibrosis pattern. That supports the notion that some of the associations presented could be limited to very extensive or progressive abnormalities, similar to changes seen in interstitial lung disease that are known to be associated with lung cancer [10, 11]. Finally, while our findings suggest that ILA preceded the diagnosis of lung cancer in the AGES-Reykjavik study, and we excluded cancer diagnoses that were present on participant entry, we cannot exclude the possibility that some slowly growing lung cancers could have occurred coincident with, or preceded the development of, ILA in some participants.

Despite these limitations, these findings have several implications for further research. The associations presented here between ILA and lung cancer indicate that studies and theories investigating the biological relationship between cancer and fibrotic lung diseases such as IPF could extend their approach to earlier stages of pulmonary fibrosis. In addition, the increased risk of lung cancer among people with ILA could, if replicated in studies of other populations, suggest that early fibrotic changes of the lung such as ILA should be considered as a risk factor in lung cancer screening.

In conclusion, ILA were found to be associated with an increased hazard of lung cancer diagnosis as well as increased mortality from lung cancer. Such associations were not found for non-pulmonary malignancies.

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