Development and Progression of Interstitial Lung Abnormalities in the Framingham Heart Study

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Abstract

Rationale: The relationship between the development and/or progression of interstitial lung abnormalities (ILA) and clinical outcomes has not been previously investigated.

Objectives: To determine the risk factors for, and the clinical consequences of, having ILA progression in participants from the Framingham Heart Study.

Methods: ILA were assessed in 1,867 participants who had serial chest computed tomography (CT) scans approximately 6 years apart. Mixed effect regression (and Cox) models were used to assess the association between ILA progression and pulmonary function decline (and mortality).

Measurements and Main Results: During the follow-up period 660 (35%) participants did not have ILA on either CT scan, 37 (2%) had stable to improving ILA, and 118 (6%) had ILA with progression (the remaining participants

without ILA were noted to be indeterminate on at least one CT scan). Increasing age and increasing copies of the *MUC5B* promoter polymorphism were associated with ILA progression. After adjustment for covariates, ILA progression was associated with a greater FVC decline when compared with participants without ILA (20 ml; SE, ± 6 ml; $P = 0.0005$) and with those with ILA without progression (25 ml; SE, ± 11 ml; $P = 0.03$). Over a median follow-up time of approximately 4 years, after adjustment, ILA progression was associated with an increase in the risk of death (hazard ratio, 3.9; 95% confidence interval, 1.3–10.9; $P = 0.01$) when compared with those without ILA.

Conclusions: These findings demonstrate that ILA progression in the Framingham Heart Study is associated with an increased rate of pulmonary function decline and increased risk of death.

Keywords: idiopathic pulmonary fibrosis; interstitial lung disease; interstitial lung abnormalities; *MUC5B*; progression

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At a Glance Commentary

Scientific Knowledge on the

Subject: Cross-sectional studies have demonstrated that interstitial lung abnormalities (ILA) are associated with increased respiratory symptoms, physiologic decrements, genetic abnormalities, and an increased risk of death suggestive of an early and/or mild form of pulmonary fibrosis. Although the longitudinal imaging findings of those with ILA in lung cancer screening trials have been presented, there has been no prior evaluation of the rates of ILA development and progression in the general population. The risk factors for, and the outcomes associated with, ILA progression are not known.

What This Study Adds to the

Field: This study demonstrates that 6% of the adult participants in the Framingham Heart Study either developed or had progression of ILA over an approximately 6-year period. Compared with those without ILA, those with ILA progression were older, had increasing copies of the *MUC5B* promoter polymorphism, experienced an accelerated decline in their measures of forced vital capacity, and had an increased rate of mortality in follow-up.

Interstitial lung abnormalities (ILA) have been defined as radiologic abnormalities on chest computed tomography (CT), commonly associated with interstitial lung disease or pulmonary fibrosis (1, 2), when present in a research participant without a clinical diagnosis. To date, primarily cross-sectional analyses, have demonstrated that research participants with ILA are more likely to have respiratory symptoms (1, 2) and physiologic decrements including reduced lung volumes (1–3), exercise capacity (4), diffusion capacity of carbon monoxide (2, 5), and an increased risk of death (6). However, there has been no study that has attempted to determine if the progression or development of ILA, defined by serial chest CT examinations, is associated with adverse clinical outcomes.

We hypothesized that radiologic progression in research participants with, or

in those who develop, ILA would be associated with an accelerated rate of physiologic decline and an increased rate of mortality. To test these hypotheses, we assessed 1,867 participants from the Framingham Heart Study (FHS) who had two chest CT scans that were separated by an average interval of 6 years. Based on these findings additional analyses were performed to determine if particular demographic, physiologic, radiologic, or genetic factors were associated with the development and/or progression of ILA. Some of the results of this study have been previously reported in the form of an abstract (7).

Methods

Study Design

The FHS, which began in 1948 and now includes several cohorts, is a longitudinal study originally designed to identify epidemiologic risk factors for cardiovascular disease; this analysis included assessments of the Third Generation and Offspring cohorts (8, 9). We previously published data on the epidemiologic and genetic associations of 2,633 adults recruited from the Third Generation and Offspring Cohorts who participated in the FHS-MDCT2 (Multidetector Computed Tomography 2) study from November 2008 to April 2011 (2). In addition to questionnaires, physical examinations, and measurements of respiratory physiology, participants in the FHS-MDCT2 study completed a volumetric, inspiratory, chest CT (Discovery VCT 64 PET/CT; GE Healthcare, Waukesha, WI) covering the whole lung.

For the current study, we additionally analyzed data on 1,867 of these same adults who had previously participated in the FHS-MDCT1 (Multidetector Computed Tomography 1) study from June 2002 to April 2005. In addition to questionnaires, physical examinations, and measurements of respiratory physiology, participants in the FHS-MDCT1 study completed an ECG-gated, inspiratory, cardiac CT (Lightspeed; GE Healthcare) covering the lung from approximately the level of the carina to the level of the diaphragm.

Our primary analysis of serial pulmonary function measures included the results of spirometric examinations

obtained closest to the date of the CT scan. On average pulmonary function testing was done within 1 year of the CT scan. Mortality was ascertained as of December 2013 resulting in a median follow-up time of 4.0 years from the completion of the FHS-MDCT2 study. *MUC5B* promoter polymorphism genotyping (rs35705950) in the FHS was performed using Taqman Genotyping Assays (Applied Biosystems, Foster City, CA), as described previously (2).

The FHS-MDCT studies were approved by the institutional review boards at Boston University Medical Center, Massachusetts General Hospital, and the Brigham and Women's Hospital and all participants provided written informed consent including consent for the use of their DNA in genetic studies.

CT Evaluation

CT scans were evaluated in three stages. First, using a previously described sequential reading method (*see the online supplement*) (1, 2, 10), up to three readers (including radiologists and pulmonologists) independently scored each CT scan for the presence of ILA who were blind to prior radiologic interpretations of the same participant, interpretations of other readers, or any participant-specific information. ILA on CT scans were defined as nondependent changes affecting more than 5% of any lung zone including any combination of nondependent ground-glass or reticular abnormalities, diffuse centrilobular nodularity, nonemphysematous cysts, honeycombing, or traction bronchiectasis. CTs with either focal or unilateral ground-glass attenuation, focal or unilateral reticulation, or patchy ground-glass abnormality (<5% of the lung) were considered indeterminate (2).

Second, to provide further detail on the radiologic characteristics of ILA, we identified the pattern of ILA (*see online supplement*) (1). We then created additional ILA subsets defined by those with or without pulmonary parenchymal architectural distortion diagnostic of a fibrotic lung disease (definite fibrosis) (2, 11), and we further characterized these scans into those with or without a usual interstitial pneumonia (UIP) pattern (as defined by American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin

American Thoracic Association criteria) (12). All ILA subtyping was performed by a consensus of three readers blind to any additional participant-specific information or prior CT interpretation.

Third, after completing ILA phenotyping and subtyping, all participants with ILA present on at least one of either the initial (cardiac) CT or the subsequent (thoracic) CT had both sets of images simultaneously compared. Paired CTs were initially scored on a five-point scale (definite regression, probable regression, no change, probable progression, and definite progression). Progressive change was defined as an increase in lung areas affected with nondependent ground-glass, reticular abnormalities, diffuse centrilobular nodularity, nonemphysematous cysts, honeycombing, or traction bronchiectasis, or a new appearance of at least one such abnormality. All paired CT evaluations were performed by a consensus (with majority voting in

discordant cases) of three readers blind to any additional participant-specific information.

Statistical Analysis

All analyses with ILA progression as the outcome variable were performed using generalized estimating equations to account for familial correlation as previously described (13), and the multivariable analyses were additionally adjusted for covariates (including age, sex, body mass index, and smoking behavior) where indicated (*see online supplement*). Mixed effect linear regression models were used to evaluate the association between ILA and measures of lung function decline as measured by the difference in lung function at two consecutive examinations divided by the length of time (in yr) between examinations, with a random effect to account for familial correlation. To evaluate the association between ILA and mortality, we used both generalized

estimating equations with logistic link and Cox proportional hazards models for models evaluating time-to-mortality, with robust variance estimates. In Cox models, all variables were assessed, and none violated the proportional hazards assumption. All genetic analyses performed used an additive genetic model (14). Reported *P* values were two-sided and those less than 0.05 were considered as statistically significant. R version 2.15.3 was used for analyses.

Results

For this analysis 1,867 FHS participants were included who had completed two sequential chest CT scans as part of their participation in both the FHS-MDCT1 and the FHS-MDCT2 studies (mean difference, 6.4 yr; SD, 0.8 yr; median difference, 6 yr; interquartile range, 0.9 yr). The workflow describing the blinded imaging characterizations of the CT scans

Figure 1. Workflow and results of computed tomography (CT) scan reading by CT scan timing and ILA status. The *top row* shows the results of FHS-MDCT1 by ILA status. Directly *below* is a depiction of what percentage from each ILA category remained the same or changed between FHS-MDCT1 and FHS-MDCT2, and if the ILA status changed what change occurred. Next, the results of FHS-MDCT2 are shown by ILA status. Finally, the results of the sequential comparison are shown, divided into improving/stable ILA and developing/progressive ILA. FHS-MDCT1 = Framingham Heart Study Multidetector Computed Tomography 1 Study; FHS-MDCT-2 = Framingham Heart Study Multidetector Computed Tomography 2 Study; ILA = interstitial lung abnormalities.

from these two studies is described in Figure 1 and Table E1 in the online supplement. Baseline characteristics of the participants with ILA, indeterminate ILA status, and without ILA are presented in either Table E2 (when defined by the FHS-MDCT1 images) or have been presented previously (when defined by the FHS-MDCT2 images) (2). Of the 1,867 participants with sequential chest CT scans, 155 (8%) had ILA on at least one of the two sets of CT scans, and 660 (35%) participants did not have ILA on either CT scan (1,052 [56%] participants did not have ILA on either CT scan but were noted to have indeterminate status on at least one of their CT scans) (see Table E3). Of the participants with ILA on either CT scan, the predominant radiologic pattern of ILA was a subpleural reticular pattern (occurring in 44 of 53 cases [83%] from MDCT1, and in 103 of 134 cases [77%] from MDCT2) (see Tables E4–E6).

After the initial blinded characterization, the 155 sets of chest CTs noted to have ILA were sequentially characterized for ILA development and progression on a five-point scale. Of these 155 sequential pairs of chest CT scans, 32 (21%) had definitely progressed, 86 (55%) had probably progressed, 24 (15%) had stayed the same, nine (6%) had probably improved, and four (3%) had definitely improved. For ease of exposition and to

provide meaningful comparisons, those who developed or had progressive ILA (ILA with progression, including 118 participants with probable and definite progression, 6% of the total 1,867 participants) were compared with those with stable or improving ILA (ILA without progression, including 37 participants with no change, or probable and definite improvement, 2% of the total 1,867 participants) and with those without ILA (660 participants, 35% of the total 1,867 participants). Baseline and clinical characteristics of these three groups are presented in Table 1. When compared with those without ILA, those with ILA with progression were older, had a greater history of tobacco smoke exposure, and were more likely to have increasing copies of the minor allele of the *MUC5B* promoter polymorphism (rs35705950). When compared with those with ILA without progression, those with ILA with progression were older, had a reduced body mass index, and were less likely to be actively smoking despite similar degrees of tobacco smoke exposure overall.

Sequential Chest CT Imaging Comparisons

First, we evaluated longitudinal imaging characteristics of the FHS participants noted to have ILA on their initial chest CT. Of the 1,867 initial chest CTs evaluated, ILA were noted in 53 (3%) of the participants,

830 (44%) were noted to be indeterminate, and 984 (53%) did not have ILA. Of the 53 participants with ILA on their initial chest CT, five (9%) had definite fibrosis and none were noted to have a UIP pattern (as defined by American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association criteria) (12). Of the 53 participants with ILA on their initial CT scan, over approximately 6 years 32 (60%) had ILA on their follow-up CT scan of which 23 (72% of 32, or 43% of 53) had progressed (including all five of the participants initially noted to have definite fibrosis). Of the 23 participants in the FHS with ILA noted on their initial chest CT who developed progressive imaging abnormalities, 21 (91%) ultimately had definite fibrosis (Figure 2A, 1–6) of whom two (9%) had developed a UIP pattern (Figure 2B, 1–6). Of the 53 participants with ILA on their initial CT scan, over approximately 6 years 30 (57%) were either stable (nine, 30%) or improved (21, 70%).

Second, we sought to determine the imaging characteristics of the FHS participants who developed ILA over the approximately 6-year follow-up period. Of the 1,867 subsequent chest CTs, ILA was noted in 134 (7%), 763 (41%) were indeterminate, and 970 (52%) did not have ILA. Of the 134 cases of ILA, 102 (76%) were not identified on the evaluation of

Table 1. Baseline Characteristics of Participants in the FHS-MDCT1 and FHS-MDCT2 Studies Stratified by ILA Status*

	No ILA (n = 660; 35%) (1)	ILA without Progression (n = 37; 2%) (2)	ILA with Progression (n = 118; 6%) (3)	P Values			
				All†	1 vs. 2‡	1 vs. 3§	2 vs. 3
Age, yr	49 ± 10	58 ± 11	65 ± 11	<0.0001	<0.0001	<0.0001	<0.0001
Sex, female, n (%)	296 (45)	20 (54)	53 (45)	0.6	0.3	0.96	0.3
Race, white, n (%)	660 (100)	37 (100)	118 (100)	—	—	—	—
Body mass index	28 ± 6	30 ± 6	28 ± 5	0.01	0.006	0.91	0.005
Pack-years smoking	16 ± 16	26 ± 19	24 ± 21	<0.0001	0.003	0.0001	0.7
Current smokers, n (%)¶	48 (7)	9 (25)	6 (5)	0.004	0.001	0.2	0.07
Former smokers, n (%)	263 (40)	14 (39)	61 (52)				
Never smokers, n (%)	349 (53)	13 (36)	51 (43)				
<i>MUC5B</i> genotype, n (%)							
G/G	529 (80)	27 (73)	78 (66)	0.0003	0.5	<0.0001	0.1
G/T	125 (19)	10 (27)	36 (31)				
T/T	6 (1)	0	4 (3)				

Definition of abbreviations: FHS-MDCT = Framingham Heart Study Multidetector Computed Tomography; ILA = interstitial lung abnormalities.

*Values are means ± SD unless otherwise indicated. For time-dependent covariates (e.g., age, body mass index, pack-years of smoking, and current smoking status) information obtained closest to the MDCT1 scan is included.

†P values are for the comparison among all groups. All P values are calculated using generalized estimating equations to account for familial relationships in the FHS.

‡P values are for the comparison between no ILA and ILA without progression.

§P values are for the comparison between no ILA and ILA with progression.

||P values are for the comparison between ILA without progression and ILA with progression.

¶P values presented are for the comparison of current smokers with former smokers and with never smokers.

Figure 2. Sequential chest computed tomography (CT) images of three participants; each panel (A–C) represents a different participant. In each panel, images 1–3 are representative axial cuts from MDCT1 and images 4–6 are representative axial cuts from MDCT2. In all panels, images 1 and 4 are at the level of the carina, images 2 and 5 are at the level of the right inferior pulmonary vein, and images 3 and 6 are at the base of the lungs. (A) Interstitial lung abnormalities (ILA) in MDCT1 (images 1–3) that progressed over a period of 7 years to ILA with definite fibrosis in MDCT2 (images 4–6), for which definite fibrosis is defined as pulmonary parenchymal architectural distortion diagnostic of fibrotic lung disease. (B) ILA in MDCT1 (images 1–3) that progressed over approximately 6 years to a usual interstitial pneumonia pattern of fibrosis in MDCT2 (images 4–6). (C) Indeterminate ILA status in MDCT1 (images 1–3) that progressed over 5 years to a usual interstitial pneumonia pattern of fibrosis in MDCT2 (images 4–6). MDCT1 = Framingham Heart Study Multidetector Computed Tomography 1 Study; MDCT-2 = Framingham Heart Study Multidetector Computed Tomography 2 Study.

the initial chest CT. In reviewing these 102 ILA cases, 95 (93%) were noted to have progressive imaging abnormalities and represented newly developed cases of ILA, whereas seven (7%) were unchanged (in review of serial images these cases were believed to have been misclassified as not having ILA during our initial blinded evaluation). Of the 95 newly developed ILA cases, 12 (13%) had already developed definite fibrosis and one (1%) had developed a UIP pattern (Figure 2C, 1–6). Workflow describing the sequential comparisons, and subtyping of participants with ILA and individual level progression data, can be found in Tables E3–E6.

The *MUC5B* Promoter Polymorphism and Progressive Imaging Abnormalities

Next, we sought to determine if the minor allele of the *MUC5B* promoter polymorphism (rs35705950) was independently associated with progressive imaging abnormalities. When compared with those without ILA, in a multivariable model (adjusted for age, sex, body mass index, pack-years smoking, current smoking status, *MUC5B* genotype, and baseline FVC), only the *MUC5B* genotype and age remained significantly associated with progressive imaging abnormalities (see Table E9). For example, for each copy of the *MUC5B* promoter polymorphism there was an 180% increase in the odds of having progressive imaging abnormalities (odds ratio [OR], 2.8; 95% confidence interval [CI], 1.7–4.4; $P = 0.0001$) and for each additional year older the odds of having progressive imaging abnormalities increased by 14% (OR, 1.14; 95% CI, 1.11–1.17; $P < 0.0001$), when compared with those without ILA. When participants with

ILA on the initial CT scan were excluded, the *MUC5B* genotype and age remained significantly associated with progressive imaging changes (see Table E10). When compared with participants with ILA without progression in a multivariable model, no predictors, including the *MUC5B* promoter polymorphism, were significantly associated with having progressive imaging abnormalities (see Table E11).

Progressive Imaging Abnormalities and Pulmonary Function Decline

Subsequently, we sought to determine if progressive imaging abnormalities were associated with an accelerated rate of lung function decline. To perform these analyses, we initially compared changes in serial measures of spirometry that were performed closest to the corresponding serial chest CT evaluations. Participants without ILA had a mean decrease in FVC of 35 ml (SD ± 44 ml) per year, those with ILA without progression 40 ml (SD ± 44 ml) decrease per year, and ILA with progression had a mean decline of 64 ml (SD ± 51 ml) per year.

As demonstrated in Table 2, compared with those without ILA, and with those with ILA but without progressive imaging abnormalities, those with progressive imaging abnormalities had evidence for an increased rate of decline in their measures of FVC, (after adjusting for age, sex, body mass index, and smoking behavior). Compared with those without ILA, those with progressive imaging abnormalities had a 20-ml greater loss in FVC per year (20 ml; SE, ± 6 ml; $P = 0.0005$) after adjusting for covariates (age, sex, body mass index, and smoking behavior). Compared with those with ILA but without

progressive imaging abnormalities, those with progressive imaging abnormalities had a 25-ml greater loss in FVC per year (25 ml; SE, ± 11 ml; $P = 0.03$) after adjusting for covariates. There continued to be evidence for an association between ILA and FVC decline in analyses where ILA was limited to those without definite fibrosis on either scan when compared with no ILA (18 ml; SE, ± 6 ml; $P = 0.005$). Additional analyses related to specific ILA subtypes and comparisons with those indeterminate for ILA status are included in Tables E7 and E8, and Figure E1.

Next, we sought to determine if the accelerated FVC decline noted among those with ILA with progression was limited to the period of radiologic progression or if it preceded it. To perform these analyses, we compared serial changes in measures of spirometry performed in intervals that corresponded to periods preceding the serial chest CT evaluations. After adjustment for covariates, when compared with participants without ILA and with those with ILA without progression, there was no evidence that those with ILA with progression had an accelerated FVC decline in any interval preceding the serial chest CT evaluations (see Table E12).

Progressive Imaging Abnormalities and Mortality

Finally, we sought to determine if those with progressive imaging abnormalities had an increased risk for mortality in a subsequent follow-up period. Over a median 4-year follow-up period subsequent to the FHS-MDCT2 study, 8% (10 out of 118) of participants with ILA with progression had

Table 2. Association of ILA Progression with Change in Spirometry Relative to Participants without ILA*

	ILA with Progression Compared with No ILA				ILA with Progression Compared with ILA without Progression			
	Unadjusted Analysis	P Value	Adjusted Analysis [†]	P Value	Unadjusted Analysis	P Value	Adjusted Analysis [†]	P Value
FEV ₁ decline, ml/yr	13 $\pm$ 4	0.005	14 $\pm$ 5	0.005	9 $\pm$ 9	0.3	14 $\pm$ 10	0.2
FVC decline, ml/yr	29 $\pm$ 5	<0.0001	20 $\pm$ 6	0.0005	22 $\pm$ 11	0.04	25 $\pm$ 11	0.03
FEV ₁ /FVC, change, %	−0.2 $\pm$ 0.07	0.004	−0.06 $\pm$ 0.07	0.4	−0.1 $\pm$ 0.1	0.3	−0.08 $\pm$ 0.16	0.6

Definition of abbreviation: FHS = Framingham Heart Study; ILA = interstitial lung abnormalities.

*P values for all analyses, both adjusted and unadjusted, are calculated using general linear models to account for familial relationships in the FHS. No ILA, n = 579; ILA without progression, n = 28; and ILA with progression, n = 72. Values are linear regression coefficients $\pm$ SE, representing the additional decline in spirometry in participants with ILA with progression versus the comparison group.

[†]Adjusted analyses include additional adjustments for age, sex, body mass index, pack-years smoking, and current smoking status.

died, as compared with 3% (1 out of 37) of those with ILA without progression and 1% (5 out of 660) of the participants without ILA (includes all participants with no ILA on both CT scans). When compared with those without ILA, those with progressive imaging abnormalities had an approximately 2.9-fold increase in their risk for death (hazard ratio [HR], 3.9; 95% CI, 1.3–10.9; $P=0.01$) and an approximately threefold increase in their odds of dying (OR, 4.3; 95% CI, 1.4–13.3; $P=0.01$) over a median 4-year follow-up period after adjusting for covariates (age, sex, body mass index, and pack-years smoking) (Figure 3). Similar results were seen when ILA with progression was subset to exclude those who either had or developed definite fibrosis (HR, 5.4; 95% CI, 1.5–19.3; $P=0.01$). When compared with those with ILA without progressive imaging findings, there was no evidence of increase in the risk of, or odds for, death in the follow-up period (HR, 1.6; 95% CI, 0.2–12.2; $P=0.6$; and OR, 2.0; 95% CI, 0.3–14.3; $P=0.5$). Additional analyses with respect to mortality and those with indeterminate status (but without ILA) on either CT evaluation are presented in the online supplement.

Discussion

Our study, which presents the first blinded comparison of serial chest CTs for the purpose of identifying ILA development and progression, demonstrates a number of important findings. First, we demonstrate over an approximately 6-year follow-up period, the development and progression of ILA can be commonly observed in the general population. Second, we identify genetic (*MUC5B* promoter genotype), and demographic (e.g., age) risk factors for progressive imaging abnormalities. In addition, it is worth noting that although progressive imaging abnormalities in the FHS are more common among those with increased exposure to tobacco smoke, a significant number of those with progressive imaging abnormalities were never smokers. Finally, we demonstrate that progressive imaging abnormalities are associated with important physiologic (e.g., accelerated rate of lung function decline) and clinical (e.g., increased rate of mortality) consequences. To date, these findings provide the most complete picture of the risk factors for, rates of development

and progression of, and adverse outcomes associated with imaging abnormalities suggestive of an early and/or mild form of pulmonary fibrosis.

Although prior longitudinal studies evaluating ILA have not been performed in general population samples, have not included blinded comparisons of large numbers of serial chest CTs, and have not reported clinical outcomes, there have been three prior studies that have evaluated ILA progression in chest CTs obtained for lung cancer screening trials (5, 15, 16). The prevalence of ILA in these studies ranged from 3% to 10% (5, 16) with estimates of progression ranging from 20% at 2 years (5) to 46% at 4 years (16). These findings are comparable with our findings, which noted that ILA was prevalent on 3% of the initial scans of which 43% demonstrated progressive imaging abnormalities over approximately 5 years of follow-up time. Our presentation of the progression of ILA to imaging findings consistent with UIP in 4% (present in 2 of the 53 follow-up scans initially identified as having ILA) is also consistent with prior reports (5, 15). However, our study suggests that because prior reports have only followed up the chest CTs of participants initially noted to have ILA, it is likely that these studies have missed important numbers of participants with progressive imaging abnormalities (including those that can develop a UIP pattern *de novo*) over a relatively short time frame.

In addition, we provide some evidence for factors that help predict progressive imaging abnormalities. Given the strong association between advanced age and idiopathic pulmonary fibrosis (IPF), the most common form of interstitial lung disease in general (17), the associations between advanced age and progressive imaging abnormalities are not very surprising. The association between *MUC5B* promoter genotype and progressive imaging abnormalities is worth further discussion. The association between the minor allele of the *MUC5B* promoter polymorphism (rs35705950) and IPF is among the most well-replicated findings of genetic association in pulmonary medicine (18). Somewhat unexpectedly, increasing copies of the minor allele of rs35705950 have also been associated with reduced mortality among patients with IPF, suggesting that the *MUC5B* variant defines a mild subtype of IPF (19).

Figure 3. Kaplan-Meier survival curves comparing participants without ILA, participants with ILA without progressive imaging, and participants with ILA with progressive imaging. Follow-up for the mortality analyses (time zero) begins at MDCT-2, the second computed tomography scan used for sequential comparisons. ILA = interstitial lung abnormalities; MDCT-2 = Framingham Heart Study Multidetector Computed Tomography 2 Study.

Our findings demonstrate that there is an increased mortality rate associated with progressive imaging abnormalities, which are also associated with increasing copies of the *MUC5B* promoter genotype (findings consistent with our prior association between *MUC5B* and ILA in cross-sectional analyses) (2). In total, these findings could suggest that the prior association between *MUC5B* genotype and improved mortality in patients with IPF (19) might be explained, in part, by a survivorship bias. Alternately, it is possible that although the *MUC5B* genotype may be correlated with an increased rate of mortality in the general population through an increased risk of developing pulmonary fibrosis, among patients with IPF specifically, there may be other important genetic and/or environmental risk factors that are even more deleterious.

Finally, our study, for the first time, presents evidence demonstrating that there are important physiologic and clinical consequences to the development and/or progression of ILA. Compared with those without ILA, and with those with ILA without progression, participants with ILA with progression experienced an accelerated decline in their measures of FVC. For example, compared with those without ILA, those with progressive imaging abnormalities had slightly less than twice the annual rate of decline in their measures of FVC over an approximately 6-year interval. Our findings also demonstrate that this accelerated lung function decline is a phenomenon that coincides with the period of progressive imaging changes. It should be noted that although the annual rate of decline in measures of pulmonary function among those with ILA with progression is less than that experienced by patients with IPF in clinical trials (20, 21), the annual rate of decline in measures of pulmonary function is comparable with that experienced by smokers

who develop chronic obstructive pulmonary disease (22). Furthermore, participants in the FHS who developed and/or had progression of ILA were more likely to die in a subsequent 4-year follow-up interval. Although our study cannot definitely determine the cause of death in participants with progressive imaging abnormalities in this cohort, these findings provide at least one missing piece of the prior puzzling association between the development of a restrictive lung deficit and an increased rate of mortality in the general population (23).

Our study has several limitations. First, although both blinded and subsequent simultaneous comparisons of serial chest CT images demonstrate the development and progression of ILA in the FHS, we also demonstrate that misclassification can occur in blinded assessments (primarily caused by the inability to detect ILA when the most prominent abnormalities are present in regions of the lung not covered by cardiac CT images). In addition, we cannot rule out the possibility that differences in imaging protocols (e.g., differences in slice thickness) (24, 25), specifically the relative increase in slice thickness of the cardiac CT scans, may have led to underestimation of ILA, and could have contributed to misclassification. Second, although we use a process of voting to resolve differences when determining phenotypes derived from consensus of three readers, we cannot rule out the possibility that dominant voices could influence the opinions of the group. Third, because the comparisons for progression were done side by side of different CT scan techniques, which did not allow for blinding the temporality of the CT scans, we cannot completely rule out potential bias in progression scoring.

Fourth, although we were able to demonstrate that FHS participants with

progressive imaging abnormalities had an accelerated rate of lung function decline when compared with those without ILA and with those with ILA but without progressive imaging abnormalities, small numbers of participants with ILA but without progressive imaging abnormalities, and with ILA with specific subtypes, limits the power to perform some comparisons. Fifth, we cannot rule out the possibility that selection attrition (caused by death or study dropout in those participating in the FHS-MDCT1 but not the FHS-MDCT2 studies) could have influenced our findings. Finally, despite the fact that we have demonstrated that progressive imaging abnormalities are associated with an accelerated lung function decline, it is important to note that our study cannot definitely determine if progressive imaging abnormalities are directly related to the increased rate of mortality noted in these participants. It remains possible that progressive imaging abnormalities could be correlated with a unique disorder, or a set of disorders, that are more directly correlated with mortality.

In conclusion, our study demonstrates that the development and/or progression of ILA over an approximately 6-year follow-up period is associated with accelerated lung function decline and an increased rate of mortality in the general population. These progressive imaging findings are more common among older people and among those with increasing copies of the minor allele of the *MUC5B* promoter polymorphism. Although the morbidity and mortality associated with IPF is well described (26), our study suggests that earlier stages of pulmonary fibrosis may also have important clinical consequences. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

References

1. Washko GR, Hunninghake GM, Fernandez IE, Nishino M, Okajima Y, Yamashiro T, Ross JC, Estépar RS, Lynch DA, Brehm JM, *et al.*; COPDGene Investigators. Lung volumes and emphysema in smokers with interstitial lung abnormalities. *N Engl J Med* 2011;364:897–906.
2. Hunninghake GM, Hatabu H, Okajima Y, Gao W, Dupuis J, Latourelle JC, Nishino M, Araki T, Zazueta OE, Kurugol S, *et al.* *MUC5B* promoter polymorphism and interstitial lung abnormalities. *N Engl J Med* 2013;368:2192–2200.
3. Lederer DJ, Enright PL, Kawut SM, Hoffman EA, Hunninghake G, van Beek EJ, Austin JH, Jiang R, Lovasi GS, Barr RG. Cigarette smoking is associated with subclinical parenchymal lung disease: the Multi-Ethnic Study of Atherosclerosis (MESA)-lung study. *Am J Respir Crit Care Med* 2009;180:407–414.
4. Doyle TJ, Washko GR, Fernandez IE, Nishino M, Okajima Y, Yamashiro T, Divo MJ, Celli BR, Sciurba FC, Silverman EK, *et al.*; COPDGene Investigators. Interstitial lung abnormalities and reduced exercise capacity. *Am J Respir Crit Care Med* 2012;185:756–762.
5. Tushima K, Sone S, Yoshikawa S, Yokoyama T, Suzuki T, Kubo K. The radiological patterns of interstitial change at an early phase: over a 4-year follow-up. *Respir Med* 2010;104:1712–1721.
6. Putman RK, Hatabu H, Araki T, Gudmundsson G, Gao W, Nishino M, Okajima Y, Dupuis J, Latourelle JC, Cho MH, *et al.*; Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) Investigators; COPDGene Investigators. Association

- between interstitial lung abnormalities and all-cause mortality. *JAMA* 2016;315:672–681.
7. Putman RK, Araki T, Hatabu H, Gao W, Dupuis J, Latourelle JC, Nishino M, Zazueta OE, Kurugol S, Ross JC, *et al.* Development and progression of interstitial lung abnormalities in the Framingham Heart Study [abstract]. *Am J Respir Crit Care Med* 2016;193:A4283.
 8. Splansky GL, Corey D, Yang Q, Atwood LD, Cupples LA, Benjamin EJ, D'Agostino RB Sr, Fox CS, Larson MG, Murabito JM, *et al.* The Third Generation Cohort of the National Heart, Lung, and Blood Institute's Framingham Heart Study: design, recruitment, and initial examination. *Am J Epidemiol* 2007;165:1328–1335.
 9. Kannel WB, Feinleib M, McNamara PM, Garrison RJ, Castelli WP. An investigation of coronary heart disease in families. The Framingham offspring study. *Am J Epidemiol* 1979;110:281–290.
 10. Xu JF, Washko GR, Nakahira K, Hatabu H, Patel AS, Fernandez IE, Nishino M, Okajima Y, Yamashiro T, Ross JC, *et al.*; COPDGene Investigators. Statins and pulmonary fibrosis: the potential role of NLRP3 inflammasome activation. *Am J Respir Crit Care Med* 2012;185:547–556.
 11. Lee HY, Seo JB, Steele MP, Schwarz MI, Brown KK, Loyd JE, Talbert JL, Schwartz DA, Lynch DA. High-resolution CT scan findings in familial interstitial pneumonia do not conform to those of idiopathic interstitial pneumonia. *Chest* 2012;142:1577–1583.
 12. Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, Colby TV, Cordier JF, Flaherty KR, Lasky JA, *et al.*; ATS/ERS/JRS/ALAT Committee on Idiopathic Pulmonary Fibrosis. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med* 2011;183:788–824.
 13. Uh HW, Wijk HJ, Houwing-Duistermaat JJ. Testing for genetic association taking into account phenotypic information of relatives. *BMC Proc* 2009;3:S123.
 14. Seibold MA, Wise AL, Speer MC, Steele MP, Brown KK, Loyd JE, Fingerlin TE, Zhang W, Gudmundsson G, Groshong SD, *et al.* A common MUC5B promoter polymorphism and pulmonary fibrosis. *N Engl J Med* 2011;364:1503–1512.
 15. Sverzellati N, Guerci L, Randi G, Calabrò E, La Vecchia C, Marchianò A, Pesci A, Zompatori M, Pastorino U. Interstitial lung diseases in a lung cancer screening trial. *Eur Respir J* 2011;38:392–400.
 16. Jin GY, Lynch D, Chawla A, Garg K, Tammemagi MC, Sahin H, Misumi S, Kwon KS. Interstitial lung abnormalities in a CT lung cancer screening population: prevalence and progression rate. *Radiology* 2013;268:563–571.
 17. American Thoracic Society; European Respiratory Society. This joint statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS) was adopted by the ATS board of directors, June 2001 and by the ERS Executive Committee, June 2001. *Am J Respir Crit Care Med* 2002;165:277–304.
 18. Putman RK, Rosas IO, Hunninghake GM. Genetics and early detection in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2014;189:770–778.
 19. Peljto AL, Zhang Y, Fingerlin TE, Ma SF, Garcia JG, Richards TJ, Silveira LJ, Lindell KO, Steele MP, Loyd JE, *et al.* Association between the MUC5B promoter polymorphism and survival in patients with idiopathic pulmonary fibrosis. *JAMA* 2013;309:2232–2239.
 20. King TE Jr, Bradford WZ, Castro-Bernardini S, Fagan EA, Glaspole I, Glassberg MK, Gorina E, Hopkins PM, Kardatzke D, Lancaster L, *et al.*; ASCEND Study Group. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *N Engl J Med* 2014;370:2083–2092.
 21. Richeldi L, du Bois RM, Raghu G, Azuma A, Brown KK, Costabel U, Cottin V, Flaherty KR, Hansell DM, Inoue Y, *et al.*; INPULSIS Trial Investigators. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. *N Engl J Med* 2014;370:2071–2082.
 22. Fletcher C, Peto R. The natural history of chronic airflow obstruction. *BMJ* 1977;1:1645–1648.
 23. Mannino DM, Buist AS, Petty TL, Enright PL, Redd SC. Lung function and mortality in the United States: data from the First National Health and Nutrition Examination Survey follow up study. *Thorax* 2003;58:388–393.
 24. Araki T, Nishino M, Gao W, Dupuis J, Washko GR, Hunninghake GM, Murakami T, O'Connor GT, Hatabu H. Anterior mediastinal masses in the Framingham Heart Study: prevalence and CT image characteristics. *Eur J Radiol Open* 2015;2:26–31.
 25. Araki T, Nishino M, Gao W, Dupuis J, Putman RK, Washko GR, Hunninghake GM, O'Connor GT, Hatabu H. Pulmonary cysts identified on chest CT: are they part of aging change or of clinical significance? *Thorax* 2015;70:1156–1162.
 26. American Thoracic Society. Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. American Thoracic Society (ATS), and the European Respiratory Society (ERS). *Am J Respir Crit Care Med* 2000;161:646–664.