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LUNG CANCER SCREENING:

RADIOLOGICAL ASPECTS BEYOND THE PULMONARY NODULE

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INTRODUCTION

Major advances over the last decade in the performance of computed tomography (CT) have revolutionized the ability of radiologists to detect the most subtle subclinical manifestations of disease. This has prompted a number of large scale CT screening studies of the chest for the early detection of diseases such as lung cancer. So far, large scale acceptance and implementation of these types of screening programs has been ampere primarily by a lack of demonstrated benefit on disease survival.[1,2]

Early detection of lung cancer can theoretically result in a substantial reduction of mortality, but it may also induce socalled lead-time bias or overdiagnosis bias. In fact, a meta-analysis of three international studies on spiral CT screening showed a more than 3-fold increase of lung cancer diagnosis but no reduction of mortality at 5 years, compared to the expected figures in that population.[3] Recently, the analysis of the first randomised trial on CT screening has demonstrated identical lung cancer mortality in the two arms, at three year follow-up.[2] The most convincing explanation of all these results is that radiologic imaging can detect slow-growing or "indolent" lung cancer at a much earlier stage, but is unable to intercept the fast-growing or "most aggressive" disease before the onset of metastases.

Nevertheless, lung cancer screening trials offer the unique opportunity to investigate the smoking-induced pulmonary diseases on large study populations. Smoke is related to a wide spectrum of diseases other than lung cancer, such as pulmonary emphysema, airways disease, interstitial lung disease and coronary disease. Although these abnormalities, whether clinically significant or not, are commonly regarded as incidental findings in a lung cancer screening setting, their evaluation might provide either important information on their prevalence and crucial insights for the comprehension of their pathogenesis and link with lung cancer.

While debate continues about the efficacy of CT screening for early lung cancer detection in broad populations of smokers, some parallels investigations are aiming to assess whether a combination of radiological, clinical, genetic and proteomic analyses of the pulmonary inflammatory processes

occurring in the lungs of smokers can identify a subpopulation of them with higher individual risk of lung cancer.[4-6] Definition of individual risk can reduce the target population for screening and prevention programs, and allow focussing on the various modalities of intervention, depending on specific profiles of biologic risk. Identification of common pathways for pulmonary inflammation and lung cancer may improve the efficacy of prevention and treatment strategies against chronic tobacco-related pulmonary diseases.

In 2005, a randomised lung cancer trial, called Multicentric Italian Lung Detection trial (MILD), was launched at National Cancer Institute of Milan. A three-years long review of the CT examinations of the MILD participants has been performed to explore the following issues:

1) the emphysema features: sex differences
2) the intertstitial lung diseases: prevalence, appearances and evolution over time
3) the airways diseases: bronchial diverticula

MILD POPULATION AND INVESTIGATIVE PROCEDURES

The MILD project is a population-based randomized, controlled, lung cancer screening trial, whose primary end-point is the assessment of smoking cessation percentage and the ultimate impact of early lung cancer detection on mortality. Eligibility criteria include age ≥ 49 yrs, ≥ 20 pack years smoking history, no history of cancer within the prior 5 years.

The population of volunteers was recruited among respondents to advertisements and articles published in the lay press and from television broadcasts. All volunteers were assessed for their eligibility and asked to sign a consent form, including a detailed information sheet to participate in the study. The trial was approved by the Institutional Review Board and by the Ethics Committees of the centres taking part in the project.

Participants were randomised in two groups: a control group which underwent a programme of primary prevention with pulmonary function test evaluation and blood sample collection, and an early detection group where periodic spiral CT is performed with primary prevention, pulmonary function evaluation and blood sample collection. The early detection group is further randomised in two arms: yearly low-dose CT versus CT every 2 yrs.

Participants were asked in advance to allow a couple of hours for completion of the questionnaire, physical examination, blood sampling, lung function test and spiral CT. The questionnaire included detailed information on smoking history and the presence of respiratory symptoms and previous treatment of selected diseases including cancer, physician-diagnosed chronic bronchitis and asthma

Pulmonary function tests

Forced vital capacity (FVC) and forced expiratory volume at 1 second (FEV_1) were measured at baseline in all study participants by using an electronic spirometer that utilises a brass Fleisch type pneumotachometer (PDS Research UK Ltd, Kent, UK) connected to a computer for

the analysis of data according to the recommendations of the American Thoracic Society and the European Respiratory Society.[7] For each session a 3 L syringe was used to calibrate spirometer equipment.

CT scanning protocol

CT was performed with a 16-detector CT scanner (Somatom Sensation; Siemens Healthcare, Forchheim, Germany) without contrast material (0.75-mm collimation, 0.5-second rotation time, 1.5 pitch, 30 effective mAs, and 120 kVp). The acquisition field of view ranged from 300 to 400mm. The same parameters were adopted for each repeat scan. The entire chest was scanned in full inspiration in about 10 seconds by using a craniocaudal scanning direction. For each examination, images were obtained from the raw data by using the following parameter settings: 1-mm-thick sections at 1-mm increments (reconstruction kernel B50f) and 5-mm-thick sections at 5-mm increments (one with kernel B50f and one with kernel B30f).

Emphysema assessment

All MDCT scans were transferred to a separate PC workstation and analyzed for emphysema assessment by a seven year-experienced thoracic radiologist (NS). For this purpose, a prototypical software (MeVis Research, Bremen, Germany),[8] was used. Briefly, this software allowed the application of high-precision 3D image analysis tools to volumetric MDCT data providing, both for the whole lung and each pulmonary lobe, a convenient assessment of MDCT parameters, such as: pulmonary volumes, mean lung density (MLD), 15th percentile point (defined as the cut off value in Hounsfield units [HU] below which 15% of all voxels are distributed), emphysema proportion (using an upper threshold of -950 HU), and distributional features of emphysema (i.e. core or peel predominance in the whole lung, with the peel region defined as the peripheral 10 mm lung area and the remaining area defined as the core region). The emphysematous regions were further categorized according to their volumes. The 3D emphysematous volumes were sorted as following:

2 to 8 mm3 (class 1); 8 to 65 mm3 (class 2); 65 to 120 mm3 (class 3); and >120 mm3 (class 4), modified from Blechschmidt et al.[9] The lower limit of 2 mm3 in the smallest cluster was used to minimize the influence of noise on the evaluation. A 3x3 kernel-based axial Gauss smoothing was applied to minimize the noise in sharp kernel images.

GENDER DIFFERENCES IN EMPHYSEMA PHENOTYPE IN SMOKERS WITHOUT AIRFLOW OBSTRUCTION

Men and women seem to respond differently in type and localization of lung damage due to tobacco exposure, suggesting that the nature of biologic injury may differ with genders.[10] In COPD, female smokers are more likely than men to exhibit small airway disease, whereas men are prone to develop a more severe emphysematous phenotype.[11-13] However, emphysema is highly variable in smokers and is not necessarily associated with COPD.[14,15] Previous epidemiologic studies have been mostly limited to COPD, giving therefore a limited view as to the epidemiology of emphysema. Radiologic investigations targeting gender-related differences are in their infancy, and further investigations are warranted.

Pursuing a more precise phenotypic-gender definition of the emphysema component through MDCT has the potential to improve our understanding of the pathogenesis and underlying biological mechanisms of emphysema. Further attention on gender-related emphysema phenotype may also provide more insight into different susceptibility to tobacco smoke and relative pathophysiologic consequences.

In this retrospective analysis on a lung cancer screening population, we have explored how gender influences emphysema phenotype, by using an advanced tool for emphysema measurement in a large, prospectively studied cohort of smokers without clinical evidence of airflow obstruction. Our goals were to determine (1) whether gender differences in emphysema phenotype are different from those observed in COPD patients; and (2) whether gender influences the relationship between emphysema and other variables such as age, smoking history and functional decline.

METHODS

The study group consisted of 1,011 smokers (recruited consecutively by the Multicentric Italian Lung Detection [MILD] project at the Istituto Nazionale Tumori of Milan between September 2005 and December 2007), whose baseline low-dose CT scans were available for the emphysema assessment.

All demographic and pulmonary function data, smoking history and emphysema assessment were recorded. Subjects were classified in to modified Global Initiative for Chronic Obstructive Lung Disease staging.[16] Since spirometric data was only pre-bronchodilator, subjects with a FEV1/FVC ratio < 0.7 were excluded from the study.

As for emphysema assessment, we used CT images reconstructed for detection of pulmonary nodules: 1-mm-thick sections with a reconstruction increment of 1 mm and a sharp kernel (Siemens B50 kernel).

Statistical analysis

Transgender comparisons were made by Student t test or $\chi 2$ testing as appropriate. Multivariate linear regression models were used to assess the relationships between gender and the dependent variables of MDCT emphysema features. The models included potential confounding effect of age, body mass index (BMI), FEV1% predicted, FVC % predicted, smoking status and number of pack-years of smoking. The significance of the interactions for the combined effect of gender with the other covariates was assessed by comparing the differences between the deviances of the models with and without the interaction term to the $\chi 2$ distribution with 1 degree of freedom. The heterogeneity test was applied to evaluate the difference between two or more estimates for gender effect to emphysema distribution and clusters. SAS Release 8.2 was used for statistical calculation.

RESULTS

Baseline demographic and clinical characteristics

The final study cohort consisted of 957 subjects (age, 58.1 ± 5.9 yr ;614 males), since 54 subjects were excluded from the original study group because of a FEV1/FVC ratio lower than 0.7. Demographic and pulmonary function data, smoking history and MDCT emphysema features are tabulated against gender in Table 1. All subjects were white Caucasians. Ten subjects (1%) had lung cancer detected by low-dose MDCT. Women were slightly younger than men, with a slightly lower body mass index (BMI), and reported a milder smoking history (Table 1). Women, compared with men, exhibited similar FEV1% (P = 0.22), higher FVC% predicted levels (P = < 0.0001), but lower levels of FEF25-75 % predicted (P = < 0.0001) and FEV1/FVC ratio (P = 0.03). These associations were not substantially modified after adjusting for age, pack-years, and whole-lung emphysema proportion; thus, men had significantly lower levels of FVC % predicted (-7.45%, 95% CI: -9.66, -5.24; P < 0.0001) and higher levels of FEF25-75 % predicted (0.90% greater, 95% CI: 0.07, 1.04; P < 0.0001).

Emphysema assessment

All the MDCT emphysema measurements were less severe in female than in male smokers (P < 0.0001) (Table 1). Such differences were evident in the univariate models and in most cases apparently larger in multivariate models after adjustment for age, BMI, smoking status, pack years of smoking, FEV1% and FVC%. Table 2 summarizes the differences between men and women for all variables considered. Both the MLD and the 15th percentile point were greater in women (P < 0.0001). The proportion of emphysema in women was lower in the whole lung , both in the core and peel regions. However, as shown by transgender differences for the core/peel ratio, the pattern of emphysema on the axial plane slightly differed between genders, as women showed a lower proportion of emphysema in the core of the lung compared to the peel, whereas the reverse was true

in men ($P < 0.0001$) (Fig. 1). We observed that the gender differences in lobar emphysema proportion were heterogeneous: in women, emphysema proportion was lower in each lobe ($P < 0.0001$), but such differences were greater in the middle lobe and in the upper lobes compared to the lower lobes ($P = 0.004$) (Fig. 2). Table 2 also summarizes multivariate regression analyses of the emphysematous areas sorted by size. Both women and men showed similar proportion of the smallest clusters ($P > 0.05$), although men displayed a significantly greater proportion of the bigger clusters, with the greatest one being reported for the class 4 clusters (on average 1.31% higher; 95% CI: 0.89-1.73; $P < 0.0001$) (Fig. 1).

Relationship between emphysema and clinical features

In the multivariate models, we observed significant interactions between gender and the other covariates, namely age, BMI and FEV1% predicted (Fig. 3). Based on these interaction analyses, both in men and women the proportion of whole lung emphysema increased with age. This increase was higher in women and women older than 68 showed no difference in emphysema extent compared to men (Fig. 3A). As FEV1% predicted levels decreased, the whole-lung emphysema proportion tended to increase more rapidly in women than men, and women with a FEV1% predicted lower than 76.2% had a greater emphysema proportion than men (Fig. 3B). The total emphysema proportion tended to increase with the decrease of BMI, and the increase was more rapid in men. These data suggest that women tended to have lower emphysema proportion than men, particularly in non overweight subjects (BMI over 40) (Fig. 3C). Despite the significant interaction between gender and FVC% predicted ($P < 0.0001$), women seemed to maintain a lower whole-lung emphysema proportion compared to men (within the range of the FVC% predicted levels analyzed). An interaction between pack-years and gender was also observed ($P = 0.02$), and in men the whole lung emphysema negatively correlated with pack-years. However, there was no interaction between smoking status and gender. On the other hand, former smokers exhibited a greater emphysema extent compared to both male and female current smokers ($P < 0.0001$).

DISCUSSION

This analysis demonstrates gender-specific differences in radiological features of emphysema in a large cohort of heavy smokers without airflow obstruction. We showed through low-dose MDCT that women, compared with men, exhibited an emphysema phenotype less extensive in each pulmonary lobe and characterized by smaller emphysematous areas and slightly less concentrated in the core of the lung. Our findings substantially mirror and extend those reported in patients with COPD. Thus, an analysis limited to severe emphysematous patients from the National Emphysema Trial (NETT),[13] showed that emphysema in women, relative to men, was less extensive and characterized by smaller hole size but less peripheral involvement on CT. Further, Dransfield et al.[17] demonstrated that women had less severe emphysema at all stages of COPD.

Data on the epidemiology of emphysema in "healthy" smokers is forthcoming from populations screened by lung cancer.[18-20] Both prevalence and severity of emphysema on low-dose CT have already been shown to be greater in male than in female smokers.[18,20] We characterized emphysema using objective 3D techniques on high-resolution volumetric MDCT datasets, whereas previous studies had assessed emphysema by visual score systems, which, compared to objective methods, tend to underestimate the prevalence of low-grade emphysema.[21] Limited emphysema is usually clinical insignificant; nevertheless, we specifically looked at this subgroup to verify the hypothesis that transgender differences in tobacco-smoke susceptibility exist.

Changes in the size of the emphysematous areas were reported to be useful in evaluating the pattern of progression of emphysema.[22] In our study, we found that the highest emphysematous clusters (class 4) in males represented the most striking difference amongst clusters between genders, whereas men and women showed the same proportion of the smallest clusters (class 1) (Fig. 1). Our results are in keeping with early pathologic studies demonstrating that there were no gender differences among smokers in susceptibility to microscopically assessed emphysema, whereas macroscopic emphysema was more commonly found in men.[23,24]

Differences in the distribution of emphysema may help understanding the disease pathogenesis and the variable development of COPD in smokers. In COPD it has been shown that the greater proportion of emphysema in male subjects is maintained both in the upper and the lower zones.[17] In our cohort of smokers without airflow obstruction, men showed more severe emphysema in each lobe. However, such differences were significantly higher in the upper lobes and in the middle lobe ($P < 0.0001$) (Fig. 2). This does not imply that men, compared with women, showed an emphysema with a more predominant cranial distribution as the middle lobe, the left upper lobe and both the lower lobes overlap topographically with the lower and the upper pulmonary regions, respectively. On the other hand, the novel finding of the middle lobe predominance may explain why smokers have a more homogeneous distribution of emphysema than previously thought.[25] To our knowledge, this is the first study that objectively assessed emphysema in each pulmonary lobe, and confirms on a large group of subjects that early smoking-induced emphysema tends to develop predominantly at these levels.

In women, relative to men, the emphysema was slightly less concentrated in the core of the lung (Table 1, 2, Fig. 1). This is different from what is seen in severe COPD subjects whose emphysema was less peripheral in women; because the radial distribution of emphysema may have a functional impact, it was suggested that such difference likely accounted for the lower diffusing capacity for carbon monoxide (DL_{co}) observed in women.[13] Unfortunately, we could not explore such morphologic-functional relationship as the DL_{co} was not part of our lung screening project.

Based on the ability to adjust for the whole-lung proportion of emphysema, pack-years and age, we noted a similar FEV_1% predicted but significantly lower FVC% predicted in men and lower FEF_{25-75} % predicted in women. We speculate that the lower FVC% predicted in males and the lower FEF_{25-75} % predicted in women were due to either the different emphysematous phenotype or by the greater degree of peripheral airways disease in women, whose smaller airway size may also place them at greater risk because toxic particulates may be more likely to deposit prior to reaching the

alveoli.[26] However, such interpretation is limited by the slight differences of functional levels between genders and by the lack of the MDCT assessment of the airway phenotype.

These findings suggested that women tended to develop a less severe emphysematous phenotype compared to men, but such transgender difference was less with the increase of age, and FEV_1% predicted decline (Fig. 3A, B). CT densitometry may be influenced by several factors, such as age and weight.[27] However, we observed that, holding constant the other covariates, as age increased, whole-lung emphysema proportion increased more rapidly in women than in men. Furthermore, we also observed that both the core and peel emphysema and the largest emphysematous clusters (i.e. the main transgender differences of emphysema) behaved in a similar way compared to the overall emphysema extent, namely, they tended to increase more rapidly in women than in men over time (data not shown). By contrast, in men emphysema increased more rapidly with the decrease of the BMI (Fig. 3C). The finding that emphysema extent increases while BMI decreases has been also reported in COPD and, importantly, may suggest a more severe systemic inflammatory response in smokers with greater emphysema extent.[28] Although no interactions were observed among severe COPD patients between gender and lung function,[13] our data show that, as the FEV_1% levels decreased, the emphysema extent increased more rapidly in women than in men, indicating a stronger relationship between the increase in the emphysema extent and lung function deterioration in female smokers without airflow obstruction. In addition, we demonstrated that, for a given pack-years history, men had more severe emphysema than women. Interestingly, male smokers with higher pack-years history displayed less emphysematous changes.

However, the relation between cigarette smoking and the presence of emphysema shows a rough dose-response curve between pack-years of smoking and emphysema.[15] Further, no interaction between smoking status and gender was observed and both female and male former smokers had more severe emphysema than current smokers. Although these observations are, at first sight, surprising, smoking cessation may be more common in those individuals with more extensive disease (i.e. healthy smoker effect). On the other hand, low-grade emphysema is unlikely to lead

smokers to quit, although these findings have to be interpreted cautiously due to the patient self-reported smoking status and in the absence of any objective assessment (i.e. exhaled carbon monoxide and nicotine metabolite levels).

Our study does have significant limitations. A low-dose MDCT protocol was applied due to the fact that radiations have an intrinsic risk of inducing a neoplasm. Although low-dose technique is now recognized as having no significant effect on CT quantification of emphysema,[29] this may not be negligible for our population of subjects whose lung were near-normal with limited extension of emphysema. Nevertheless, differences in both lung function test results and MLD differences would suggest the transgender differences we observed are not due to MDCT artifacts, but instead represent real findings. However, because full functional data was not available, we cannot exclude that a small minority of subjects was misclassified (individuals with restrictive defects), although there was no evidence of fibrosis on low-dose MDCT. In addition, although the analyses have been adjusted for various factors, it must be appreciated that transgender differences in emphysema phenotype may be accounted for hormonal factors, anatomical differences in airways, and different smoking habit.

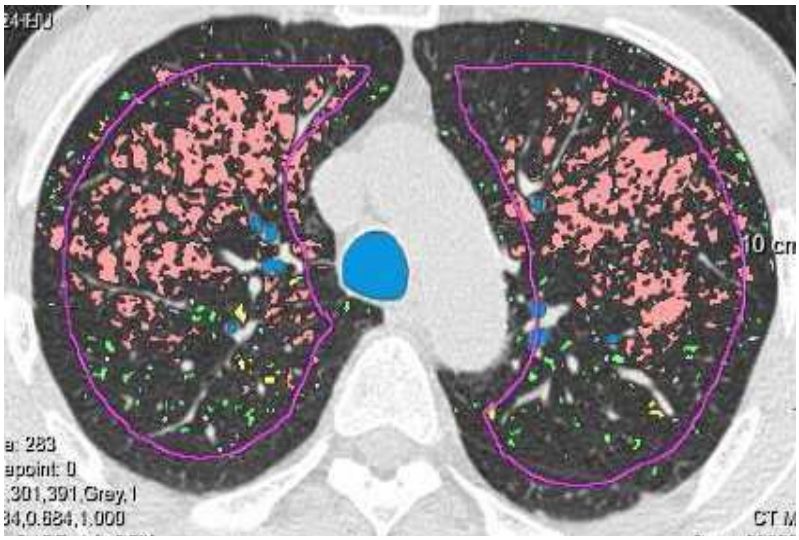
In conclusion, our study shows that gender differences exist in emphysema phenotype in subjects without COPD, thus suggesting a gender-specific pattern of early smoking-induced lung damage. In addition, we propose that transgender analysis of emphysema according to age, BMI, pack-years of smoking and FEV_1% predicted may help refining emphysema phenotypes and improve our understanding of the disease pathogenesis.

Table 1. Demographic and clinical data, smoking history, computed tomography measurements of emphysema and pulmonary function indices in women and men.

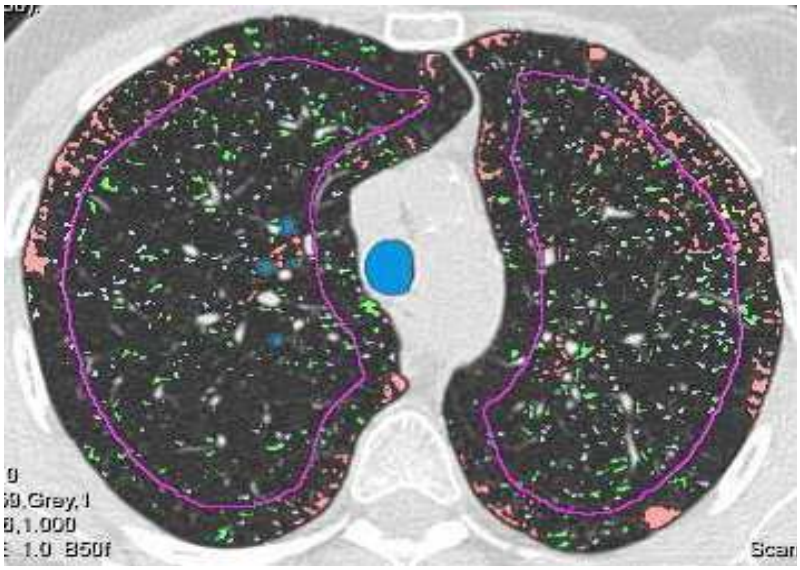
Parameter	Women (n=343) Mean (SD)	Men (n=614) Mean (SD)	*P* Value
Demographics			
Age (years)	57.56 (5.9)	58.49 (5.9)	0.02
BMI (kg/m^2)	24.45 (4.3)	26.64 (3.7)	<0.0001
Smoking history			
Duration of smoking (years)	34.92 (7.3)	37.31 (7.3)	<0.0001
Number of cigarettes per day	21.97 (8.7)	24.86 (10.9)	<0.0001
Pack-years of smoking	38.35 (17.8)	46.30 (22.1)	<0.0001
Time since cessation (years)	0.93 (3.14)	1.57 (3.05)	0.002
Smoking status			0.0007
Current smokers	266 (78.0)	414 (67.7)	
Former smokers	75 (22.0)	198 (32.3)	
Spirometry			
FEV_1	2.36 (0.5)	3.24 (0.6)	<0.0001
FEV_1 % predicted	99.33 (16.8)	97.99 (15.4)	0.2
FVC	3.12 (0.6)	4.29 (0.8)	<0.0001
FVC % predicted	111.29 (18.0)	103.31 (16.1)	<0.0001
FEV_1/FVC ratio	97.25 (11.1)	98.91 (12.2)	0.03
FEF_{25-75}% predicted	67.62 (27.2)	78.33 (31.2)	<0.0001
MDCT indices			
Lung volume (ml)	4890.91 (755.8)	6461.84 (1,055.8)	<0.0001
MLD (HU)	-829.42 (27.6)	-840.05 (25.5)	<0.0001
15thpercentile point (HU)	-914.85 (21.1)	-923.72 (17.6)	<0.0001
Emphysema proportion (%)			
Whole lung	3.71 (4.1)	4.90 (4.0)	<0.0001
Whole lung core	3.58 (4.6)	4.91 (4.4)	<0.0001
Whole lung peel	3.85 (3.8)	4.88 (3.7)	<0.0001
Core/peel ratio	0.81 (0.38)	0.93 (0.34)	<0.0001
Emphysema proportion by pulmonary lobe (%)			
Left lower	3.56 (3.8)	4.71 (4.1)	<0.0001
Left upper	4.21 (4.6)	5.74 (4.9)	<0.0001
Right lower	3.04 (4.6)	3.88 (3.7)	0.004
Right middle	4.92 (5.5)	7.12 (6.2)	<0.0001
Right upper	3.20 (4.3)	4.05 (4.1)	0.003
Emphysema proportion by cluster classes (%)			
1	0.63 (0.5)	0.80 (0.6)	<0.0001
2	0.65 (0.6)	0.94 (0.7)	<0.0001
3	0.11 (0.1)	0.16 (0.1)	<0.0001
4	1.54 (3.4)	2.20 (3.1)	0.003

Table 2. Estimated differences between men and women for computed tomography emphysema measurements by means of univariate and multivariate regression models.

MDCT variables	Univariate analysis		Multivariate analysis*	
	Estimated difference between men and women (95% CI)	*P* Value	Estimated difference between men and women (95% CI)	*P* Value
MLD (HU)	-10.63 (-14.11, -7.16)	<0.0001	-17.00 (-20.34, -13.65)	<0.0001
15th percentile point (HU)	-8.85 (-11.35, -6.35)	<0.0001	-12.75 (-15.13, -10.36)	<0.0001
Whole-lung emphysema proportion (%)	1.20 (0.66, 1.73)	<0.0001	2.00 (1.49, 2.51)	<0.0001
Whole-lung core emphysema proportion (%)	1.33 (0.74, 1.92)	<0.0001	2.10 (1.54, 2.66)	<0.0001
Whole-lung peel emphysema proportion (%)	1.03 (0.54, 1.53)	<0.0001	1.89 (1.42, 2.36)	<0.0001
Core / Peel ratio	0.12 (0.08-0.17)	<0.0001	0.10 (0.06-0.14)	<0.0001
Emphysema proportion by pulmonary lobe (%)				
Left lower	1.15 (0.62, 1.68)	<0.0001	1.91 (1.39, 2.43)	<0.0001
Left upper	1.53 (0.89, 2.16)	<0.0001	2.48 (1.86, 3.09)	<0.0001
Right lower	0.84 (0.30, 1.38)	0.0023	1.52 (0.99, 2.04)	<0.0001
Right middle	2.19 (1.41, 2.98)	<0.0001	3.10 (2.31, 3.89)	<0.0001
Right upper	0.84 (0.29, 1.40)	0.0028	1.58 (1.04, 2.12)	<0.0001
Emphysema proportion by cluster classes (%)				
1	0.166 (0.092, 0.240)	<0.0001	-0.21 (-0.42, 0.00)	0.054
2	0.288 (0.204, 0.373)	<0.0001	0.40 (0.31, 0.48)	<0.0001
3	0.050 (0.033, 0.067)	<0.0001	0.08 (0.06, 0.09)	<0.0001
4	0.663 (0.235, 1.092)	0.0025	1.31 (0.89, 1.73)	<0.0001

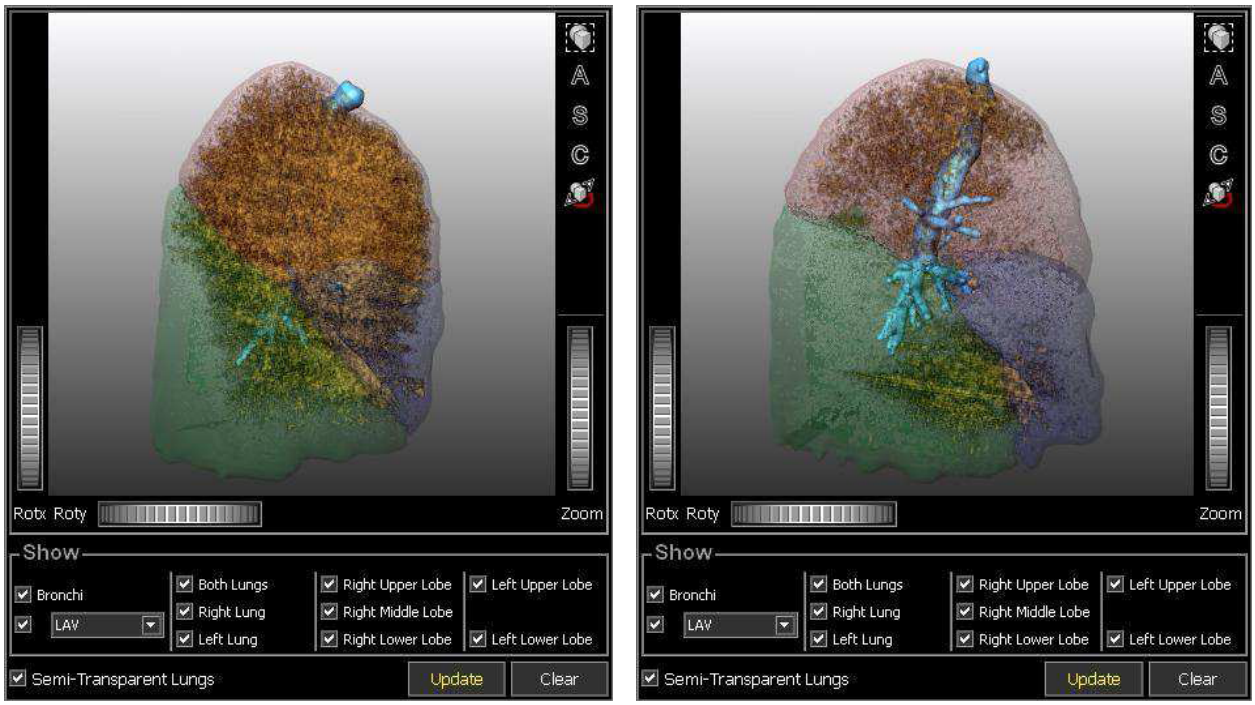


1a



1b

FIGURE 1. a) Colour-coded overlay of a multidetector computed tomography (CT) slice in the upper lobes of a 56-yr-old male showing the size distribution (cluster) of the emphysematous areas (largest clusters in purple, intermediate in yellow and smallest in green); the purple line delineates the core and the peel of the lung. Note that emphysema tends to spare the peel of the lung. **b)** CT slice of a 54-yr-old female showing a less extensive emphysema phenotype (compared with fig. 1a), predominantly characterised by smaller clusters randomly distributed throughout the lung parenchyma.



2a **2b**

FIGURE 2. 3-dimensional rendering of multidetector computed tomography (CT; lateral view of the right lung) scan with tracheobronchial tree (cyan) and middle lobe (blue), both lower lobes (green) and upper lobes (red). Inside lobes all pixels of -950 HU or less are highlighted (yellow), identifying areas of emphysema. **a)** A 68-yr-old male displays a greater emphysema proportion in each lobe compared with **b)** a 55-yr-old female, such differences are greater in the middle and upper lobes.

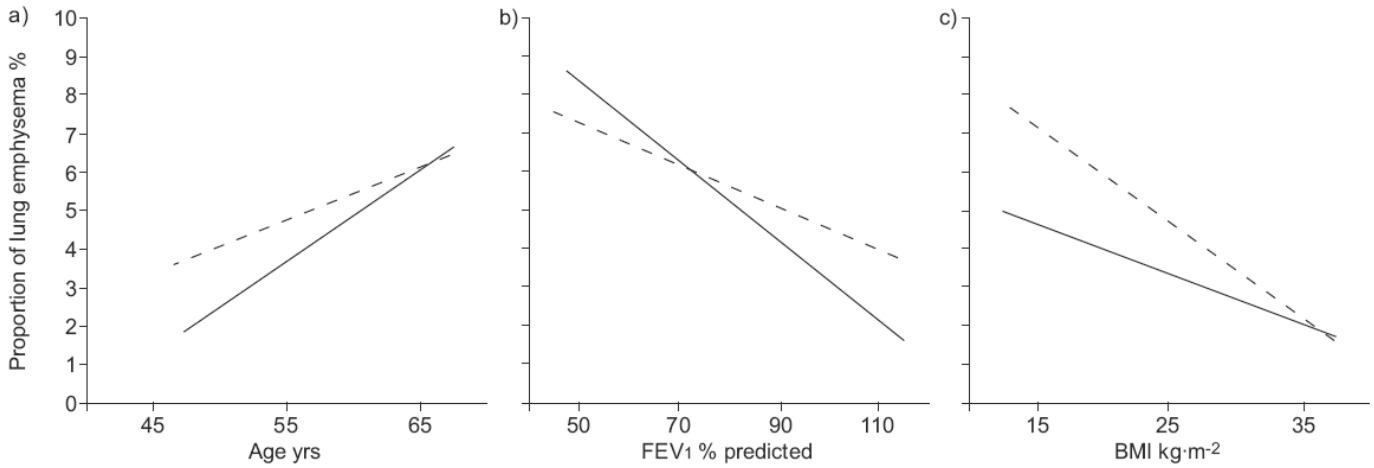


FIGURE 3. **a)** Relationship between proportion of whole-lung emphysema and age when body mass index (BMI), pack-yrs of smoking, forced expiratory volume in 1 s (FEV1) and forced vital capacity (FVC) % predicted are held constant. An interaction between age and sex is evident (p50.001). **b)** Relationship between the whole-lung emphysema proportion and FEV1 % pred when age, BMI, pack-yrs of smoking, and FVC % are held constant. An interaction between FEV1 % and sex is evident (p,0.0001). **c)** Relationship between proportion of whole-lung emphysema and BMI when age, pack-yrs of smoking, FEV1 and FVC % pred are held constant. There is a significant interaction between BMI and sex (p,0.0001). Females: ———; males: – – – –.

INTERSTITIAL LUNG DISEASES IN A LUNG CANCER SCREENING TRIAL

Cigarette smoking is a recognized risk factor for the development of interstitial lung disease (ILD).[30-32] The spectrum of thin-section CT abnormalities associated with cigarette smoking was first defined by Remy-Jardin et al.,[33,34] and since then it has been widening over years. Smoking-related thin-section CT abnormalities vary from signs of respiratory bronchiolitis in asymptomatic patients to severe fibrotic lung disease,[30-32] although the mechanisms underlying such associations are not well established. Smoking may cause subclinical parenchymal lung disease consistent with ILD detectable by CT imaging, even among apparently healthy subjects.[35]

Although the thin-section CT features of these disorders have been increasingly described in the literature, scarce data has been reported on their significance in smokers participating in a lung cancer screening trial.[36,37] A comprehensive assessment of chest CT as a screening tool should include a thorough appreciation of the prevalence and nature of these findings that may have prognostic relevance and require therapeutic interventions.

The purpose of this study was to determine the frequency, the appearances and the evolution over time of ILD by thin-section CT in a population of smokers included in a lung cancer screening trial.

METHODS

Using our local MILD electronic database, 700 subjects without lung cancer, who underwent a low-dose thin-section CT screening examination between September 2005 and June 2006 (i.e. the first year of recruitment by MILD), were selected for review. 256 out of those 700 cases were included as they had a repeat CT scan after three years according to our lung cancer screening protocol;[38] repeat CT scans were also extracted to be compared with their corresponding baseline scans. The rest of the study cases (n = 448) were randomly selected from a MILD sub-cohort of smokers included in another study addressing a separate hypothesis and mixed with the other ones.[39] Demographic data and smoking history obtained through a standardised questionnaire for MILD participants, forced expiratory volume in 1 sec (FEV_1) and forced vital capacity (FVC) expressed as percentages of the predicted value were recorded.

Image evaluation

Visual evaluations of ILD were performed on images reconstructed for detection of pulmonary nodules: 1-mm-thick sections with a reconstruction increment of 1 mm and a sharp kernel (Siemens B50 kernel). All images were viewed at window settings optimized for assessment of lung parenchyma (width, 1500–1600 HU; level, -500 to -600 HU).

The CT images of the study population were transferred to a CT workstation (Leonardo, Siemens Medical Solutions, Forchheim, Germany) and independently reviewed by two observers (NS and LG, with 7 and 4 years' experience respectively in interpreting thin-section CT scans for ILD) for the presence or absence of signs of ILD, without knowledge of the clinical data of the study population. Disagreements on presence variables and on the CT diagnosis were resolved by consensus review of divergent evaluations.

CT examinations were evaluated for the presence of parenchymal changes consistent with ILD, with the specific recommendation to record the presence or absence of ground-glass opacification, consolidation, honeycombing, reticulation and cysts, centrilobular hazy nodules and traction

bronchiectasis within areas of ILD. Observers were recommended to use the glossary of the Fleischner Society.[40]

After assessing the presence of CT findings, the observers evaluated their predominant distribution. The distribution was classified as being predominantly in the upper lung zone (when most of the findings were above the level of the tracheal carina), the lower lung zone (when most of the findings were below the level of the tracheal carina), or diffuse and as being predominantly peripheral (when findings involved mainly the outer third of the lung), central (when findings were located mainly the inner two third of the lung), or diffuse. Spatial homogeneity was evaluated through observation of a patchy versus confluent pattern.

Following the initial assessment of the CT findings, each radiologist assessed the CT patterns for each patient with CT abnormalities consistent with ILD, with the provision of specific diagnostic criteria based on the current literature and the American Thoracic Society (ATS) and European Respiratory Society (ERS) classification for the idiopathic interstitial pneumonias.[41,42] The CT findings were grouped into three CT patterns as following: 1) usual interstitial pneumonia (UIP)-like pattern, 2) nonspecific interstitial pneumonia (NSIP)-like pattern and 3) respiratory bronchiolitis (RB)-like pattern (Table 1). When the CT findings did not match any of the criteria, namely the abnormalities were equivocal for ILD (e.g. focal ground-glass opacity, unilateral reticulation etc.), the diagnosis was considered as indeterminate.

Subsequently, for each subject with a repeat CT examination after three years, the observers jointly performed a simultaneous evaluation of the baseline and the corresponding follow-up CT examinations to analyze changes over time. On the repeat CT examinations, the extent of CT abnormalities was coded as resolved, similar, greater, or lower as compared with that observed on the images obtained at baseline. The observers also assessed whether the baseline CT pattern did show any change toward another one (eg. NSIP-like pattern changed into UIP-like pattern).

Data analysis

Unweighted kappa coefficients of agreement (k) were computed for the CT patterns. Interobserver agreement was classified as poor (K = 0.00–0.20), fair (K = 0.21–0.40), moderate (K = 0.41–0.60), good (K = 0.61–0.80), or excellent (K = 0.81–1.00).[43]

Comparative analyses were obtained using both Fisher's exact test and the analysis of variance (ANOVA) to evaluate differences in selected demographic, clinical and pulmonary function test results between subjects with and those without ILD. An unconditional polytomous logistic regression model was used to assess the association between the presence of the subtypes of ILD and demographic data, clinical features and pulmonary function indices; the corresponding odds ratio (OR) with 95% confidence interval (CI) were computed. The final model included age (in continuous), sex, smoking status (current and former smokers), number of cigarettes per day (<20, 20, >20 cigarettes per day) and number of smoking years (<35, 36-39, 40 and more years). Heterogeneity among ILD subtype risks was assessed using a Wald test with 2 degrees of freedom.[44]

SAS Release 9.1 was used for statistical calculation.

RESULTS

MDCT findings at baseline

The inter-observers agreement was fair (K = 0.3) for the diagnosis of the RB-like pattern, moderate (K = 0.6) for the NSIP-like pattern, moderate (K = 0.49) for the indeterminate pattern and excellent (K = 1.00) for the UIP-like pattern.

Eight CT examinations were not considered eligible for the visual score due to motion artefacts, and the final study cohort comprised therefore 692 subjects.

At baseline, the UIP-like pattern and the NSIP-like pattern were identified in 2/692 (0.3%) and 26/692 (3.8%) patients, respectively; 109/692 (15.7%) patients showed CT abnormalities consistent with RB, while CT abnormalities equivocal for ILD were reported in 21/692 (3%) subjects. CT examinations were regarded as normal in 534/692 (77.2%) subjects.

The presence of subpleural basal honeycombing with peripheral reticular opacities and traction bronchiectasis was regarded consistent with a UIP-like pattern in 2/692 (0.3%) cases (Fig. 1). These two subjects were current smokers with a long history of smoking (40 and 50 years of smoking, respectively).

Peripheral ground-glass opacity was the most frequent finding in subjects with a NSIP-like pattern (23/26, 88%), while reticular opacities were recorded in 4 out of 26 (15.3%) cases (Fig. 2,3). In 8/26 (30.8%) cases, a NSIP-like pattern coexisted with hazy centrilobular nodules predominating in the upper zones. Small cysts intermingled with peripheral ground-glass opacity were observed in 1/26 (3.8%) case. Four out of 26 cases (15.3%) with a NSIP-like pattern showed traction bronchiectasis.

Diffuse hazy centrilobular nodules predominating the upper lung zone were the most frequent finding (97/109, 89%) in patients with a RB-like pattern. In subjects with a RB-like pattern, patchy ground-glass opacity associated with centrilobular nodules was reported in 17 out of 109 cases (15.6%) (Fig. 4,5), while ground-glass opacity was identified either as isolated finding or associated with scarce interlobular septal thickening in 8/109 (7.3%) and 4/109 (3.7%) cases, respectively.

Overall, mild interlobular septal thickening was reported in 8/109 (7.3%) cases with a RB-like pattern.

Most (19/21, 90.5%) of the indeterminate CT patterns were predominantly characterized by very mild patchy ground-glass opacities (Fig. 6). In 3 out of 19 cases (15.8%) ground-glass opacity was unilateral, while in 1/19 (5.2%) was limited to the middle lobe and the lingula. Two out of 21 (9.5%) cases showed indistinct centrilobular ground-glass opacities predominating in the upper lung zone, while another (4.8%) showed basal bilateral consolidation.

Demographic, clinical and functional findings at baseline

Demographic and smoking history, and pulmonary function data are tabulated according to the presence of ILD in Table 2. Because of the small number of cases with a UIP-like pattern, the UIP-like cases were grouped with the NSIP-like ones for the comparison analyses. Subjects with CT abnormalities either consistent or equivocal for ILD showed a longer history of smoking and were more frequently current smokers. Both subjects with a UIP/NSIP-like pattern and those with an indeterminate CT pattern were older than smokers without signs of ILD. According to the multivariate polytomous logistic regression model (Table 3), the risk for the presence of UIP/NSIP-like patterns was directly associated with age (OR 1.10; 95% CI: 1.02-1.18) and the current smoking status (OR 2.53; 95% CI: 0.88-7.32), whereas the RB-like pattern was inversely associated with age (OR 0.94; 95% CI: 0.89-0.98) and directly associated with current smoking status (OR 3.22; 95% CI: 1.63-6.35). Heterogeneity between the RB-like pattern risk and the UIP/NSIP-like pattern risk was observed for age (p=0.001), but not for smoking status (p=0.924).

Evolution between baseline and follow-up MDCT findings and smoking status

There were 256 MDCT scans after three years, with 44 (17.1%), 13 (5%) and 12 (4.7%) of them having a RB-like pattern, an indeterminate pattern and a NSIP-like pattern on baseline CT scan,

respectively. None of the subjects with a UIP-like pattern at baseline had a CT examination after three years.

Follow-up CT scan of one subject with a NSIP-like pattern at baseline was interpreted as being consistent with UIP (1/12, 8.3%) (Fig. 3). Two other cases (16.6%) with a NSIP-like pattern showed an increase in extent of the reticular abnormalities. The rest (9/12, 75%) of the repeat CT examinations of the subjects with a NSIP-like pattern did not show any changes in both the pattern and extent of the disease.

Among the 13 subjects with a indeterminate CT pattern, the CT findings were similar in 8/13 (61.5%) cases and resolved in 3/13 (23%) cases after three years. The extent of ground-glass opacity increased in 2/13 (15.4%) cases.

No RB-like patterns changed their appearance. Among the 42 subjects with centrilobular nodules at baseline, nodules were similar in 36/42 (85.7%), while they increased in profusion in 3/42 (7.1%) cases, decreased in 1/42 (2.4%) cases (Fig. 5), and completely resolved in 1/42 cases (2.4%).

Among the 9 subjects with ground-glass opacities at baseline, the extent of ground-glass opacities was similar in 7 /9 cases (77.7%), while decreased in 1/9 cases (11.1%) and increased in 1/9 (11.1%) cases, respectively. Ground-glass opacities superimposed ex novo on centrilobular nodules in only one case. One patient who had mild interlobular septal thickening at baseline, did not show any change in extent of those abnormalities at follow-up CT.

In 2 out of 184 (1.1%) smokers without any sign of ILD at baseline, diffuse peripheral ground-glass opacity resembling a NSIP-like pattern and centrilobular hazy nodules predominating in the upper zones were respectively reported. Both of them were persistent former smokers.

As detailed in Table 4, the frequency of quitters among subjects with either a NSIP-like or a indeterminate CT pattern was greater than that of those with a RB-like pattern and controls.

All the subjects with either a NSIP-like or RB-like or an indeterminate pattern showing an increase in the disease extent at repeat CT were persistent current smokers, whereas those in whom the disease extent decreased were quitters.

DISCUSSION

This study shows that abnormalities consistent with ILD are common in participants in a lung cancer screening trial, being reported in more than one quarter of our study population. This prevalence is higher than that reported by other studies evaluating the incidental findings in lung cancer screening. In the Dutch–Belgian multi-centre randomized controlled trial for lung cancer screening (NELSON study),[36] signs of pulmonary fibrosis were reported in 117/1409 (8%) cases, whereas they were observed in 6/449 (1.3%) cases recruited by the ProActive Lung Cancer Detection (PALCAD) study.[37] Such discrepancies might partly be explained by the fact that our study specifically addressed the research of the ILD and included a wider spectrum of MDCT abnormalities (eg. hazy centrilobular nodules) regarded as ILD .

Another recent study has shown by means of CT densitometric techniques in a large population-based cohort of smokers that abnormalities consistent with ILD are frequently detectable in asymptomatic smokers and cumulative and current cigarette smoking were both independently associated with them.[35] However, an advantage of our study was to assess the CT pattern among subjects with ILD to improve the discriminatory information provided by CT. To our knowledge, this is the first study that addressed such evaluation in a lung cancer screening population, and it was useful to further elucidate the incidence of the ILD in a large population of asymptomatic smokers and to explore the relevance of these CT features from a prognostic standpoint.

The findings that 2 out of 692 cases (0.3%) showed a UIP-like CT pattern at baseline and another with a NSIP-like pattern came to resemble that of UIP after three years, highlights the importance to do not overlook the presence of ILD in a lung cancer screening population. A growing body of studies shows that smoking is an independent risk factor for the development of UIP that, in the majority of the cases, carries a prognosis worse than that of many lung cancers.[45-47]Notably, the relatively low prevalence of the UIP-like CT pattern (0.4% including that case detected at repeat CT) in our study cohort was, however, slightly lower than that of the lung cancers detected by our screening project in the first year of recruitment (10/1236, 0.8%).

We reported 26/705 (3.7%) cases with a NSIP-like pattern, mainly characterized by peripheral ground-glass opacities. The coexistence of hazy centrilobular nodules in about one third of these cases further emphasizes the overlap between the ILDs' features related to smoking. The reported association between the CT abnormalities of either the NSIP-like and the UIP-like pattern and smoking status, with current smokers more at risk of developing such diseases, further corroborates the link with smoking. By contrast, the finding that the presence of a NSIP-like pattern was associated with age is in keeping with recent observations of ILD findings frequently seen among asymptomatic elderly individuals independent of smoking history.[48] However, the relevance of such MDCT abnormalities remains open to debate as 25% of the NSIP-like cases of our study showed a progression after three years, suggesting that attention should be posed even on these more apparently indolent ILDs to prevent the fibrosis progression or the occurrence of complications. Furthermore, it appears possible that abnormalities defining the NSIP-like pattern might be symptomatic as shown by the relative higher percentages of quitters smokers at follow-up among subjects with a NSIP-like pattern as compared to either controls and those with RB.

Although RB is retained a very common histologic finding in cigarette smokers as well as of little clinical significance, we have undertaken the evaluation of the CT signs of RB to extend the knowledge on their prevalence and relationship with the smoking history in a large study population. In our study, the prevalence of CT changes consistent with RB was lower than those reported previously. Whilst Remy-Jardin et al. found upper zone-predominant micronodules in 26 of 98 (27%) asymptomatic smokers,[34] we found signs of RB in 109 out of 692 (15.7%) smokers despite individuals recruited by MILD were heavier smokers. Such discrepancy may have several explanations, in particular the use of a low-dose CT protocol in our lung cancer screening trial may have lowered the detection-rate of the hazy nodules and the ground-glass opacity. Furthermore, in contrast with another study of Remy-Jardin et al. [49] who showed changes of centrilobular nodules over a mean period of 5.5 years in 11 out of 17 (64.7%) smokers, only 5 out 42 (12%) cases with centrilobular nodules displayed changes after 3 years in our study. Notably, in our study, no RB-like

pattern changed toward another one. However, the different time windows might certainly explain the differences with the study of Remy-Jardin et al.[20] In keeping with the study of Fain et al.,[50] we showed that current smokers were more at risk of showing RB as compared with former smokers, and RB findings may persist after stopping smoking, being present in both former and quitting smokers.

Our study does have some limitations, mainly the lack of histological data and a full clinical evaluation in the lung cancer screening setting induce speculation to attempt a more complete characterization of the abnormalities consistent or suspicious for ILD. Similarly to the scheme proposed by Churg and Muller,[41] the CT findings were grouped into three fundamental CT patterns (i.e. UIP-like, NSIP-like and RB-like patterns) that generally carry different prognoses. However, a significant radiological overlap exist among those CT patterns. Whilst the typical thin-section CT pattern is highly predictive of a histological diagnosis of UIP, the NSIP-like CT pattern may correspond to a wider spectrum of histological diagnoses such as desquamative interstitial pneumonia and even UIP (this might fit with our case showing NSIP-like pattern at baseline that changed the CT appearance into a UIP-like pattern after three years).[51-54] The RB-like pattern was assumed to comprise both pure RB and RB-ILD as they usually display very similar CT pattern and cannot be differentiated solely from the nature of CT abnormalities. Thus such distinction is only possible on the basis of a careful clinical evaluation that was not part of our lung cancer screening protocol. Furthermore, attempting an interpretation of the indeterminate CT patterns as well as explaining the two normal cases who developed signs of ILD at repeat CT examination would be very dangerous. Of note, no CT signs of Langerhans' cell histiocytosis were observed among the indeterminate CT patterns. Finally, we decided to evaluate only the repeat CT examinations after three years (i.e. the longest follow-up available in MILD trial) as such time window was assumed sufficient for a proper observation of the evolution of the ILD abnormalities, but, probably, a longer follow-up is needed, particularly to evaluate the NSIP-like patterns.

In conclusion, our study shows that CT signs of ILD are not uncommon in a lung cancer screening cohort and attention should be posed to their patterns to do not overlook progressive fibrosis. Our findings provide support for the hypothesis that smoking is a risk factor for those ILD.

Table 1. Diagnostic criteria for the UIP-like, NSIP-like and RB-like pattern.

MDCT pattern	MDCT findings
UIP-like pattern	Honeycombing, reticulation, no or minimal ground-glass opacity, peripheral and basal predominance.
NSIP-like pattern	Predominant ground-glass opacity, no or mild to moderate reticulation, no or traction bronchiectasis, no or minimal honeycombing, bilateral distribution.
RB-like pattern	Hazy centrilobular nodules, no or mild patches of ground-glass opacities, no or mild reticular abnormalities.
Indeterminate pattern	Unilateral distribution, predominant consolidation or cysts, and any other finding not included in the UIP-like, NSIP-like and RB-like patterns.

Table 2. Demographic and clinical characteristics of 692 subjects according to the presence of thin-section computed tomography patterns.

	RB-like pattern n=109	**NSIP and UIP-like patterns** n=28	**Indeterminate pattern** n=21	**Normal** n=534	*P*-value[1]
Age[2]	55.5 (5.4)	60.3 (6.5)	58.1 (7.1)	57.2 (5.9)	0.001
Sex[3]					
Women	36 (33.0)	4 (14.3)	4 (19.1)	185 (34.6)	
Men	73 (67.0)	24 (85.7)	17 (81.0)	349 (65.4)	0.070
Smoking status[3]					
Former smokers	11 (10.1)	5 (18.5)	3 (14.3)	159 (29.8)	
Current smokers	98 (89.9)	22 (81.5)	18 (85.7)	375 (70.2)	<.001
Number of cigarettes per day[3]					
<20	24 (22.0)	8 (28.6)	5 (23.8)	122 (22.9)	
20	46 (42.2)	7 (25.0)	10 (47.6)	230 (43.1)	
>20	39 (35.8)	13 (46.4)	6 (28.6)	182 (34.1)	0.633
Number of smoking years[3]					
<35	29 (26.6)	5 (17.9)	5 (23.8)	183 (34.3)	
35-39	32 (29.4)	8 (28.3)	6 (28.6)	125 (23.4)	
≥40	48 (44.0)	15 (53.6)	10 (47.6)	226 (42.3)	0.343
Years of stopping smoking [2]	3.8 (3.1)	3.8 (3.3)	3.5 (2.1)	5.2 (3.3)	0.438
FEV_1% [2]	93.0 (18.8)	89.0 (17.3)	98.0 (18.7)	95.3 (20.6)	0.317
FVC % [2]	101.4 (21.0)	100.8 (18.4)	106.9 (18.7)	103.8 (21.4)	0.574

[1]*P*-values derived from Fisher's exact test for categorical variables and ANOVA analysis for continuous variables.
[2]Mean value (standard deviation)
[3]Number of subjects (%)

Table 3. Odds ratio (OR) and 95% confidence intervals (CI) of interstitial lung disease for selected characteristics by computed tomography patterns.

	OR (95% CI)*			*P*-Heterogeneity
	RB-like pattern	**NSIP and UIP-like patterns**	**Indeterminate pattern**	
Age	0.94 (0.89-0.98)	1.10 (1.02-1.18)	1.03 (0.95-1.2)	0.001
Sex				
Women	1	1	1	
Men	1.12 (0.71-1.77)	2.57 (0.86-7.72)	2.38 (0.78-7.32)	0.208
Smoking status				
Former smokers	1	1	1	
Current smokers	3.22 (1.63-6.35)	2.53 (0.88-7.32)	2.79 (0.77-10.20)	0.924
Number of cigarettes per day				
<20	1	1	1	
20	0.99 (0.57-1.72)	0.73 (0.24-2.27)	1.15 (0.38-3.46)	0.409
>20	1.16 (0.65-2.08)	1.97 (0.70-5.58)	0.93 (0.27-3.22)	0.253
Number of smoking years				
<35	1	1	1	
35-39	1.38 (0.77-2.45)	2.89 (0.73-11.38)	1.34 (0.39-4.60)	0.391
≥40	1.76 (0.95-3.24)	1.76 (0.46-6.82)	1.03 (0.29-3.63)	0.589

Table 4. Evolution of smoking status between baseline and repeat computed tomography examinations.

	Persistent current smokers	Persistent former smokers	Quitting smokers	Current ex formers*
RB-like pattern	34 (77.3%)	6 (13.6%)	4 (9.1%)	0
Stable	31	6	1	
Increased	3	0	0	
Decreased	0	0	3	
NSIP-like pattern	7(58.3%)	2 (16.7%)	3 (25.0%)	0
	4	2	3	
Stable	3	0	0	
Increased	0	0	0	
Decreased				
Indeterminate pattern	7(53.9%)	2 (15.4%)	4 (30.8%)	0
	6	2	1	
Stable	1	0	0	
Increased	0	0	3	
Decreased				
Normal	123 (62.1%)	52 (26.3%)	21 (10.6%)	2 (1.0%)
Stable	123	50	21	2
Increased	0	2	0	0

**Notes – ***refers to ex-smokers who resumed smoking between baseline and repeat CT examinations.

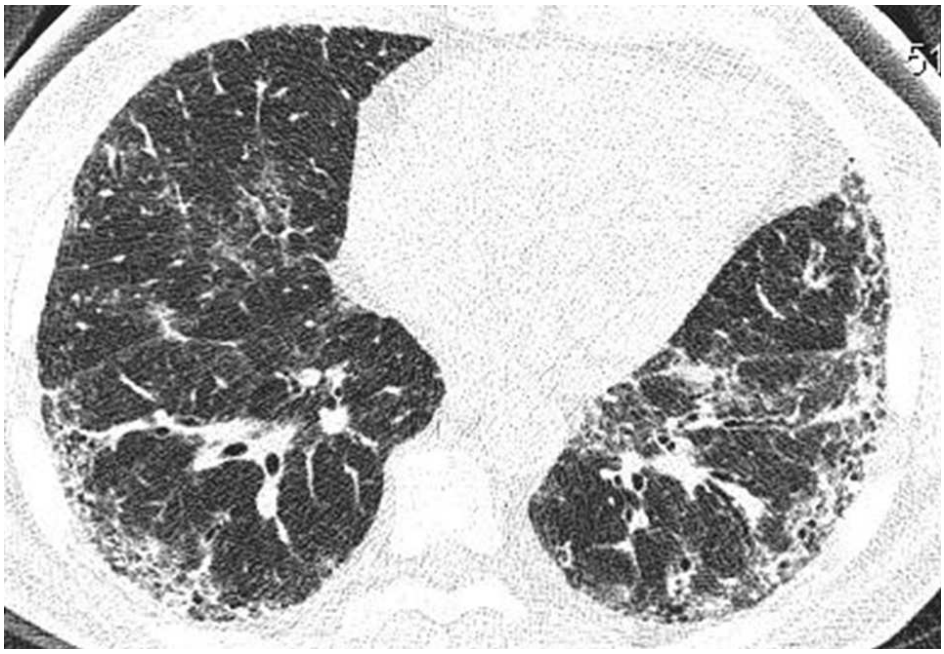


Fig. 1.A 59-year-old man with low-dose thin-section CT abnormalities resembling a UIP-like pattern. Transverse thin-section CT image shows reticular with traction bronchiectasis with minimal honeycombing, predominantly distributed in the subpleural-basal regions.

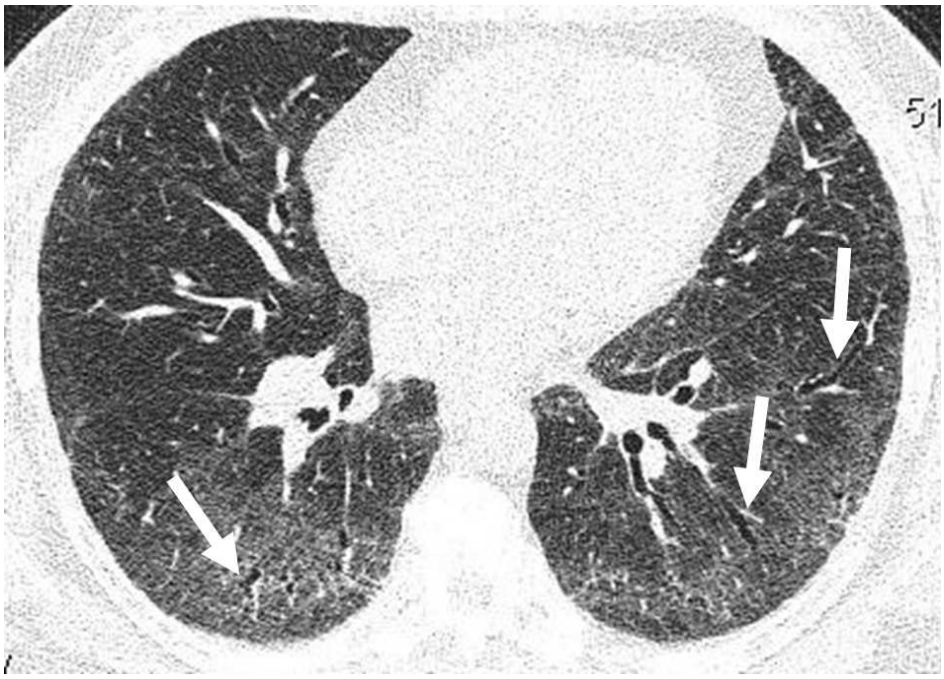
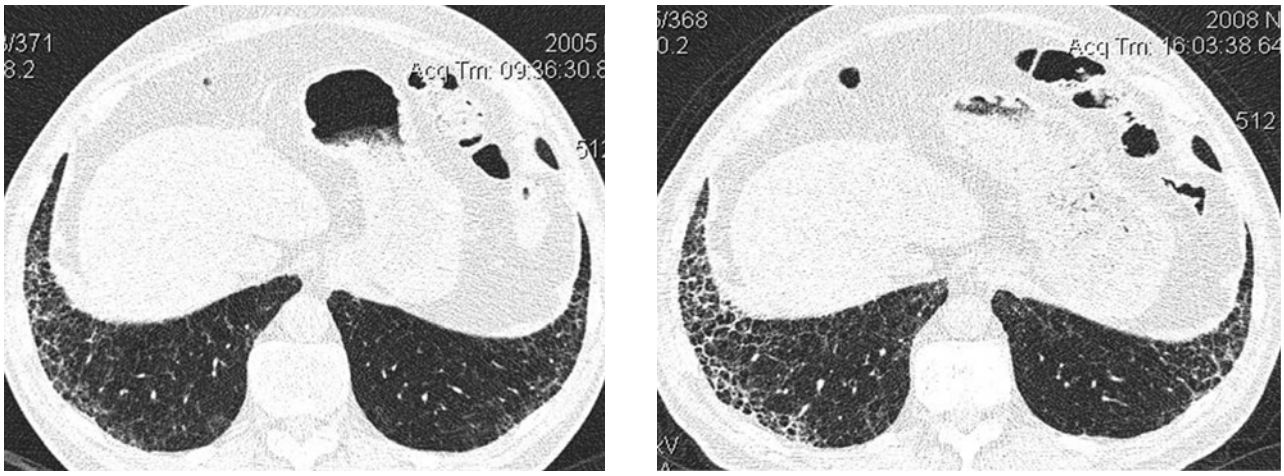


Fig. 2. Transverse low-dose thin-section CT image of a characteristic NSIP-like pattern in 64-year-old woman at the basal regions. The CT pattern is made of ground-glass opacities and minimal reticulation with intermingled mild traction bronchiectasis (arrowheads).



3(a) **3(b)**

Fig. 3. **(a)** A 52-year-old-man with low-dose thin-section CT findings regarded as a NSIP-like pattern by both the observers. Note the evident reticular opacities at the level of the basalsubpleural regions. **(b)** Repeat CT examination three years later shows increase in extent of reticulation with developed honeycombing regarded as UIP-like pattern by both the observers.

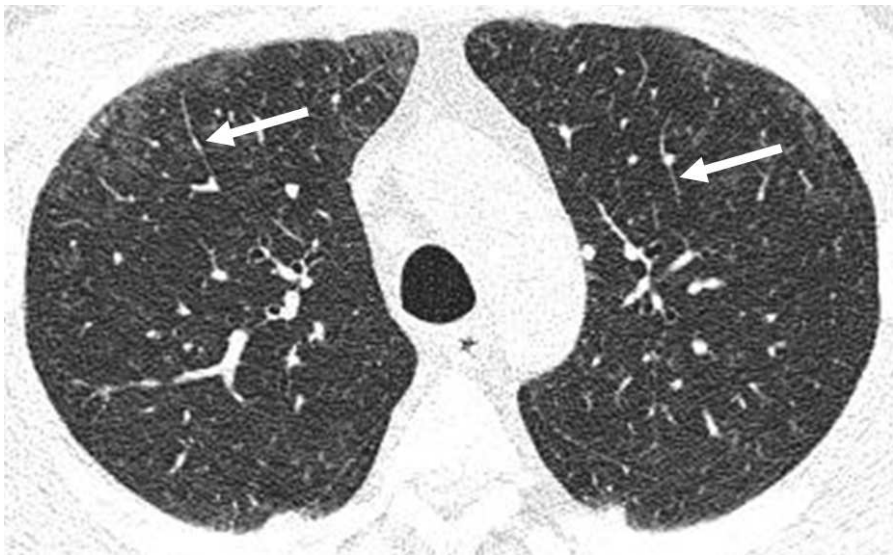
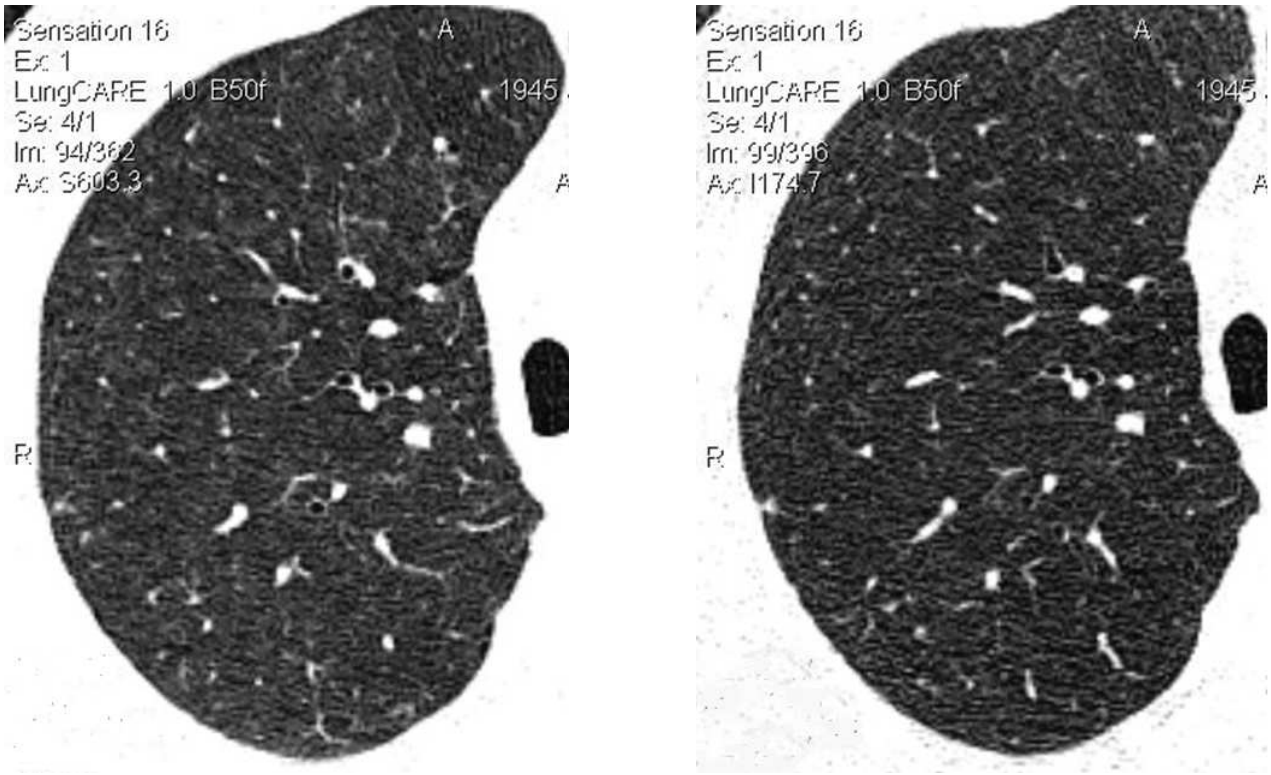


Fig. 4. A RB-like pattern in a 56-year-old woman. Low-dose thin-section CT image shows peripheral ground-glass opacity in the ventral regions, centrilobular hazy nodules, scarce interlobular septal thickening (arrows) and mild paraseptal emphysema.



5 (a) **5 (b)**

Fig. 5. Thin-section CT images in a 64-year-old quitter. **(a)** Thin-section CT image targeted to the right lung at baseline shows faint centrilobular micronodules. **(b)** Three years later, a decrease in profusion of the nodules was evident at repeat CT.

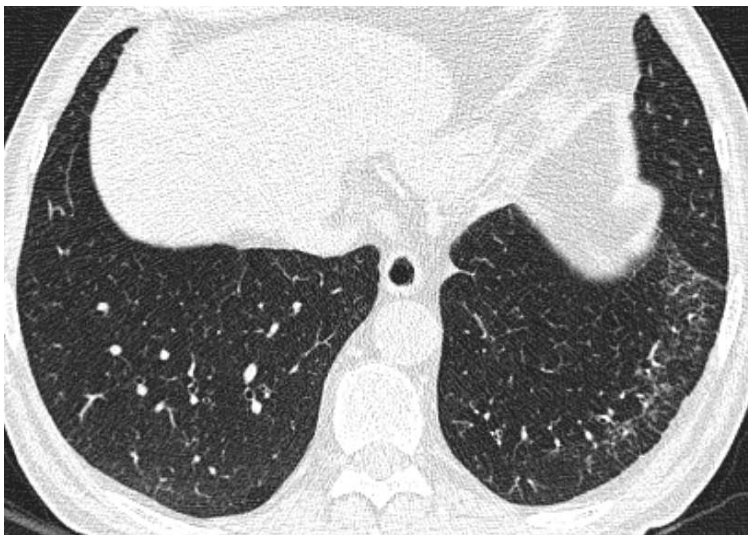


Fig. 6. A 68-year-old man with findings suspicious of interstitial lung disease, classified as CT indeterminate pattern by both the observers. Minimal ground-glass opacities are limited to the subpleural-basal regions of the left lung.

BRONCHIAL DIVERTICULA IN SMOKERS ON THIN-SECTION CT

Bronchial diverticula are thought to be rare and may be an incidental computed tomography (CT) finding. Bronchial diverticula are less well described in the literature than tracheal diverticula, which usually occur as either isolated or multiple paratracheal cysts in asymptomatic subjects, sometimes in association with Mounier-Kuhn syndrome.[55-57] Bronchial diverticula consist of dilatation of the bronchial gland ducts, which coalesce and herniate through smooth-muscle cellular bundles,[58-60] although their precise pathogenesis is incompletely understood.

Early bronchoscopic and bronchographic studies showed bronchial diverticula in about 30% of patients affected by various lung diseases (including tuberculosis, emphysema, lung cancer etc.), with chronic coughing being the most common symptom;[61,62] bronchial diverticula, however, have also been reported in normal subjects.[63] Further, an association between bronchial diverticula and chronic obstructive pulmonary disease (COPD) has been suggested.[60,64] Both chronic bronchitis and emphysema may favour the development of bronchial diverticula, presumably through the combination of bronchial wall damage and the repeated increase in intra-bronchial pressure with coughing.

Bronchial diverticula can be detected along the inner surfaces of the large bronchi, using volumetric thin-section CT. Discrete diverticula may be seen as tubular, blind-ended outpouchings arising from the bronchial walls. Sometimes, multiple bronchial diverticula give rise on thin-section CT to an "accordion-like" appearance previously described in bronchographic studies.[65] However, there are only a few reports describing bronchial diverticula on thin-section CT,[60,64-67] and no data have been published on their relationship to clinical or other morphological features.

The aim of this study was to determine the prevalence on thin-section CT of bronchial diverticula in a population of smokers and explore their relationship to emphysema, bronchial wall thickening, clinical features and functional abnormalities.

METHODS

Study population

The study group consisted of 503 smokers (recruited consecutively by the Multicentric Italian Lung Detection [MILD] project at the National Cancer Institute of Milan between December 2006 and June 2007), whose baseline low-dose CT images were available for the analysis. The study group included 267 women and 236 men with a mean age of 58.1 years (range, 49-78 years). A full smoking history was available in 485 of the 503 subjects (121 former and 364 current smokers; mean years of smoking, 37; mean number of cigarettes smoked, 23.2 per day).

Demographic data, smoking history, history of coughing during the last year, forced expiratory volume in 1 sec (FEV_1) and forced vital capacity (FVC) expressed as percentages of the predicted value, and FEV_1/FVC ratio were recorded for this study.

Bronchial diverticula grading

The thin-section CT images of the study population were transferred to a CT workstation (Leonardo, Siemens Medical Solutions) and reviewed by two observers (NS and AI, with 6 and 4 years' experience respectively in interpreting high-resolution CT images). In order to standardise the interpretation of the bronchial diverticula, defined as air-filled outpouchings arising from the bronchial walls on thin-section CT, the observers underwent a training session using 15 cases and displaying bronchial diverticula (selected by one chest radiologist with 20 years' experience, and not included in the final study population) before starting the evaluation. Subsequently, the thin-section CT images of 503 smokers were independently evaluated by the observers without knowledge of the clinical data of the study population. Axial images were reviewed with the aid of either coronal or oblique reformations. The observers were asked to report the presence and the site of the diverticula along the major bronchi (i.e. mainstem and lobar bronchi), the reformation planes through which they were visualised, and their extent. Only bronchial diverticula visualised on at least two the reformation planes were included in the final score. The extent of the bronchial

diverticula was scored according to a three-point scale: grade 0, none; grade 1 (mild), 1-3 diverticula distributed in equal or more than one bronchus (Fig; 1); grade 2 (severe), >3 diverticula distributed in equal or more than one bronchus (Fig. 2). Disagreements were resolved by a consensus review of the divergent scores.

Emphysema assessment

All MDCT images were transferred to a personal computer running MevisPULMO software, version 1.4 (MeVis Research, Bremen, Germany). Briefly, this software allows the application of high-precision 3D image analysis tools to volumetric MDCT data, providing an automated objective quantification of the emphysema.[8] A 3x3 kernel-based axial Gauss smoothing was applied to minimise the noise in sharp kernel images. The relative area of the lung with attenuation values lower than -950 H was calculated as indicating emphysema.[68] The percentage of emphysema was quantified for the whole lung.

Analysis of intra-parenchymal bronchial wall thickening

The same couple of observers assessing the bronchial diverticula, independently scored the six lobes (the lingula was regarded as a separate lobe) for the bronchial wall thickness on the axial images. Bronchial wall thickness was quantified using the visual scoring system modified by Aziz and coworkers.[69] Bronchial wall thickness was quantified relative to the adjacent pulmonary artery: grade 0, normal appearance of the bronchial walls; grade 1, trivial bronchial wall thickening (i.e. bronchial wall thickening is minimal such that no percentages of bronchial wall thickness relative to the adjacent pulmonary artery can be provided); grade 2, < 50% of the arterial diameter (Fig. 2); grade 3, 50–100% of the arterial diameter. The grading assigned to each pulmonary lobe was a subjective averaged score of the wall thickness of all the bronchi within that lobe (Fig. 2).

The total lung score used in the analysis was derived by summing the scores for each pulmonary lobe; the final scores used in the analysis were the average of the total lung scores of the observers.

Statistical analysis

Results were expressed as means, standard deviations, and as frequencies and percentages for categorical variables. Comparative analyses were obtained using the analysis of variance (ANOVA) to evaluate differences in selected demographic, clinical and pulmonary function test results among subjects with grade 1 and grade 2 bronchial diverticula and those with no bronchial diverticula. A polychotomous logistic regression model was used to assess the association between the extent of the bronchial diverticula and demographic data, clinical features, pulmonary function indices and thin-section CT features; the corresponding odds ratio (OR) with 95% confidence interval (CI) were computed. A *P* value of less than 0.05 was taken to indicate statistical significance. Interobserver agreement in the extent of bronchial diverticula and bronchial wall thickness was quantified using the Cohen's weighted kappa coefficient (K_w). Interobserver agreement was classified as poor (K_w = 0.00–0.20), fair (K_w = 0.21–0.40), moderate (K_w = 0.41–0.60), good (K_w = 0.61–0.80), or excellent (K_w = 0.81–1.00).[43] SAS Release 8.2 was used for statistical calculation.

RESULTS

Interobserver agreement was moderate (K_w = 0.5) for the extent of the bronchial diverticula and good (K_w = 0.65) for the assessment of the severity of bronchial wall thickness.

A total of 552 bronchial diverticula were visualised by all the CT reformations, whereas 72 diverticula were not included in the final score as they were seen in only one reformation plane.

Bronchial diverticula were seen in 229/503 (45.5%) subjects. Grade 1 and grade 2 bronchial diverticula were recorded in 168/229 (73.3%) and 61/229 (26.7) subjects respectively.

Most of the diverticula were detected at the level of the mainstem bronchi, with the left and the right mainstem bronchus involved in 134/503 (26.6%) and 100/503 (19.9%) cases respectively. The lingular bronchus and the right upper lobe bronchus were the most frequently involved lobar bronchi, showing diverticula in 46/503 (9.2%) and 45/503 (9%) cases respectively. The right middle

lobe bronchus, the bronchus intermedius, the left upper lobe bronchus, the left lower lobe bronchus and the right lower lobe bronchus were involved in diverticula in 38/503 (7.6%), 33/503 (6.6%), 31/503 (6.2%), 28/503 (5.6%) and 25/503 (5%) cases respectively. Most grade 1 diverticula involved 1 (97/168, 57.7%) (Fig. 1) or 2 (63/168, 37.6%) bronchi, whereas they were recorded in 3 bronchi in only 8 out of 168 cases (4.7%). On the other hand, most (46/61, 75.5%) of the grade 2 diverticula involved 3 or more bronchi, with 8/61 (13.1%) and 7/61 (11.4%) cases detected in 1 and 2 bronchi (Fig. 2) respectively.

Demographic and smoking history, pulmonary function data and CT parameters are tabulated together with the extent of bronchial diverticula in Table 1. Subjects with grade 2 bronchial diverticula showed more years of smoking, a larger number of cigarettes smoked per day, more severe functional impairment (defined by FEV_1, FVC and FEV_1/FVC ratio values), a greater extent of emphysema and more severe bronchial wall thickening compared with subjects with grade 1 and those with no bronchial diverticula ($P < 0.005$). Further, smokers with grade 2 bronchial diverticula more frequently reported a history of coughing during the previous year compared with smokers with grade 1 or those with no bronchial diverticula ($P = 0.0004$). No features other than bronchial wall thickness (more severe in smokers with grade 1 bronchial diverticula, $P < 0.0001$) differed in smokers with grade 1 bronchial diverticula and smokers without bronchial diverticula.

According to the multivariate logistic regression model, the OR for an increment of one unit of bronchial wall thickness was 1.23 (95% CI: 1.08-1.40) for subjects with grade 1 bronchial diverticula and 1.78 (95%CI: 1.46-2.17) for those with grade 2 diverticula compared with subjects with no diverticula ($P < 0.0001$) (Table 2). No other features were significantly associated with an increased risk of bronchial diverticula, although a high risk was observed for those subjects reporting coughing during the previous year (grade 1 [OR 1.70; 95% CI: 0.86, 3.38] and grade 2 bronchial diverticula [OR 2.45; 95% CI: 0.78, 7.63] compared with individuals with no diverticula).

DISCUSSION

Our study showed that bronchial diverticula are frequently encountered along the central bronchial surfaces of smokers, occurring with the highest degree of profusion in those subjects with clinical and functional markers of smoking-related damage. To our knowledge, this is the first study that specifically addressed the assessment of bronchial diverticula by reviewing CT images of a large study cohort. Polverosi et al.[67] reported five cases of diverticula located along the main bronchi, most of them occurring in association with tracheal diverticula. Sanford and Broderick[66] demonstrated with thin-section CT a case of panacinar emphysema and severe airflow obstruction associated with the presence of multiple bronchial diverticula. Grenier et al.[64] and Brillet et al.[60] reported two cases of COPD with several diverticula in the main bronchi on coronal/oblique CT reformations. According to Zompatori et al.,[65] thin-section CT images often show bronchial diverticula in patients with longstanding chronic bronchitis, whose bronchoscopic findings usually consist of erythema, copious secretions, mucosal irregularity and friability.

Identification of bronchial diverticula may be relevant in smokers. Bronchial diverticula may act as a reservoir for secretions and theoretically predispose to repeated infections of the bronchial tree. In a case report of a patient complaining of symptoms of chronic bronchitis, several diverticula, less than 2 mm in diameter, running in a straight line between the cartilages in the left main bronchus and the right middle lobe bronchus, were identified on bronchoscopy and they were associated with a large amount of purulent discharge.[70] In another case report, bronchoscopy revealed severe bronchial diverticulosis in a 12-year-old child with recurrent bronchopneumonia.[71] However, two pathological studies, reporting bronchial diverticula in patients with or without symptoms of chronic bronchitis, suggested that bronchial diverticula should not be considered as a specific component of the disease.[59,62]

In our study, smokers with grade 2 bronchial diverticula, compared with smokers with grade 1 and those with no bronchial diverticula, more frequently reported a history of coughing, suggesting a

link between bronchial diverticula and chronic bronchitis. This finding, however, has to be interpreted cautiously because of the patient's self-reported symptom status. Nevertheless, corroborative evidence comes from the fact that subjects with more profuse diverticula (grade 2) were heavier smokers and showed more severe functional impairment compared with those with no diverticula. However, no differences in clinical features were found between smokers with mild and those with no bronchial diverticula. Although the grading score of bronchial diverticula was arbitrarily computed, it would suggest that one to three diverticula located in one or two bronchi (grade 1) might represent localized disease related to either parenchymal or airway abnormalities not severe enough to cause relevant clinical changes.

Our results also suggest that bronchial diverticula parallel the inflammatory changes occurring in the smokers' lungs and airways as judged by thin-section CT. Both the extent of emphysema and bronchial wall thickening were greater in subjects with grade2 compared with subjects with grade 1 or those with no bronchial diverticula. As only bronchial wall thickening was significantly associated with an increased risk of bronchial diverticula, we speculate that bronchial wall thickening may share a common inflammatory aetiology with bronchial diverticula.

Although we did not use a gold standard such as bronchoscopy to test the accuracy of thin-section CT, volumetric thin-section CT can accurately depict bronchial diverticula, which were reproducibly identified in most cases on all the multiplanar reformatted projections. However, although multiplanar reformations may increase the confidence of the observers' evaluation, their use was only sufficient to provide a moderate interobserver agreement in the assessment of the extent of bronchial diverticula. This degree of observer variation may have several explanations, such as the increased noise inherent with the low-dose imaging, the differentiation between exaggerated bronchial corrugation and bronchial diverticulosis (Fig. 3), and the difficult assessment of the bronchial diverticula when small and located at anatomically complex sites (for example, airways bifurcations and bronchi oriented in an oblique plane). The use of the 3D reconstruction

images or the virtual bronchoscopy may be useful in the future for better morphological assessment of these bronchial diverticula.

Our study does have some limitations. Comparison with a control group of never-smokers or subjects with other diseases would have allowed a more definite assessment of the prevalence of bronchial diverticula. There is an inherent subjectivity involved in the quantitative methods used for the assessment of bronchial wall thickness. However, in support of our methods, agreement between our two observers was acceptable for such analysis. Further, it is possible that a small minority of subjects was affected by smoking-related interstitial lung diseases, which may have influenced the relationships between the clinical features and the presence of bronchial diverticula. Whilst assessing a tracheal diverticulum size may be feasible, as its mean diameter is generally 10 mm (on the axial plane),[7] we thought that this was not applicable for bronchial diverticula, which were mostly less than 2mm in diameter (data not shown). However, it is possible that large bronchial diverticula may have important clinical consequences[71].

In conclusion, our study shows that bronchial diverticula are a frequent CT finding in smokers' central bronchi and we have found relationships between them and other smoking-related CT abnormalities. As smokers with profuse diverticula exhibit unfavourable clinical features, bronchial diverticula should not be overlooked.

Table 1 – Characteristics of 503 patients according to the presence and extent of the bronchial diverticula

Characteristics	Without bronchial diverticula	Extent of bronchial diverticula		*P* value
		Grade 1	Grade 2	
Age (years)	58.16 (5.9)	58.18 (6.4)	57.57 (4.8)	0.8604
Sex				
Male	171 (62.4%)	116 (69.1%)	48 (78.7%)	
Female	103 (37.6%)	52 (30.9%)	13 (21.3%)	0.0365[3]
Smoking status				
Former	63 (23.0%)	42 (25.0%)	16 (26.2%)	
Current	203 (74.1%)	117 (69.6%)	44 (72.2%)	0.7771[3]
Missing	8 (2.9%)	9 (5.4%)	1 (1.6%)	
Smoking (years)[2]	36.74 (7.2)	36.56 (7.0)	39.68 (7.2)	0.0095
Number of cigarettes smoked[2]	22.35 (8.9)	22.63 (9.6)	28.42 (13.2)	<.0001
FEV_1%[2]	95.69 (17.6)	95.08 (18.0)	73.15 (26.8)	<.0001
FVC %[2]	106.03 (16.8)	105.43 (17.0)	94.83 (20.4)	<.0001
FEV_1/FVC ratio[2]	95.70 (14.4)	95.30 (15.5)	78.83 (20.2)	<.0001
Cough				
No	249 (90.9%)	145 (86.3%)	44 (72.1%)	
Yes	25 (9.1%)	23 (13.7%)	17 (27.9%)	0.0004[3]
Extent of emphysema (%)	5.14 (5.1)	5.91 (5.3)	8.89 (7.3)	<.0001
Intra-parenchymal bronchial wall thickness	0.95 (1.84)	1.58 (2.18)	4.48 (3.10)	<.0001

Table 2 – Odds ratio (OR)[1] and 95% confidence intervals (95% CI) of bronchial diverticula for selected characteristics by extent of the diverticula.

Characteristics		OR (95%CI)	
		Grade 1-bronchial diverticula	Grade 2-bronchial diverticula
Bronchial wall thickness		1.23 (1.08, 1.40)*	1.78 (1.46, 2.17)*
Emphysema		1.06 (1, 1.12)	1.02 (0.92, 1.15)
Sex	Men	1	1
	Women	0.75 (0.40, 1.39)	0.52 (0.16, 1.73)
Smoking status	Former smokers	1	1
	Current smokers	0.94 (0.53, 1.65)	1.76 (0.59, 5.20)
Cough	No	1	1
	Yes	1.70 (0.86, 3.38)	2.45 (0.78, 7.63)

[1]adjusted for age, number of cigarettes, forced expiratory volume in 1 sec (FEV_1), forced vital capacity (FVC), FEV_1/FVC ratio and all the variables reported in the Table
*P value <0.0001

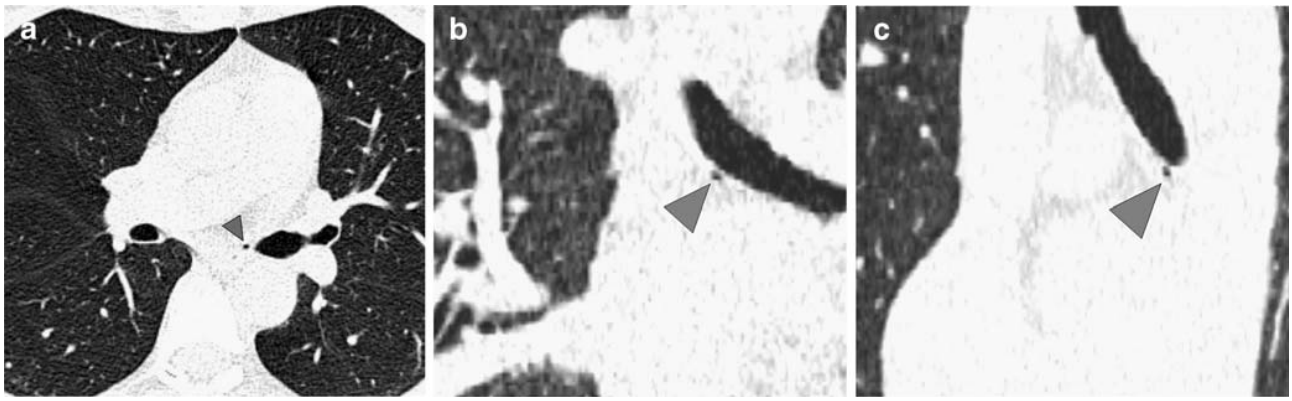


Fig. 1a–c Bronchial diverticulum in a 66-year-old male smoker. A small air collection (arrowhead) adjacent to the left main bronchus is shown on axial **(a)**, coronal **(b)** and oblique **(c)** thin-section CT reformatted images. Both the observers scored this case as grade 1.

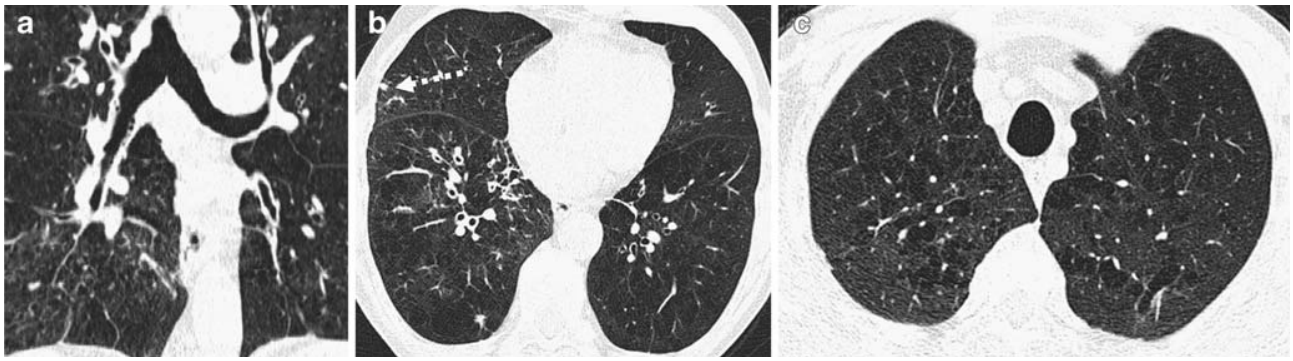


Fig. 2a–c A 62-year-old male smoker with a history of coughing. **(a)** Coronal reformatted thin-section CT image shows multiple tubular, air-filled structures (arrows) arising from the walls of the bronchus intermedius, scored as grade 2 bronchial diverticula. **(b)** Axial image shows coexisting bronchial wall thickening that was scored as grade 2 and 1 at the level of the right and left lower lobes respectively by both radiologists; mild mucus plugging is also evident at the periphery of the middle lobe (arrow). **(c)** Moderate emphysema was also present within the upper lobes.

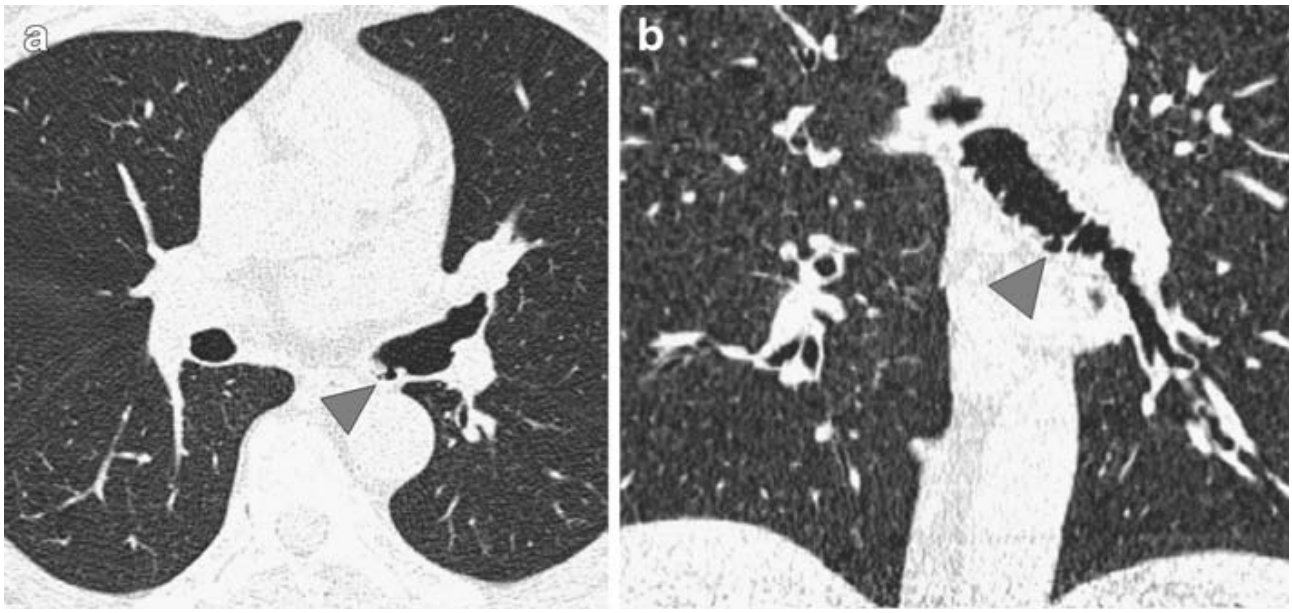


Fig. 3a, b Discordant evaluations in a case of a 69-year-old female smoker. Thin-section CT axial **(a)** and coronal **(b)** images clearly depict an air space communicating with the left main bronchial lumen (arrowhead), consistent with a bronchial diverticulum. However, the coronal image also shows a corrugated contour of the bronchial wall that was interpreted as grade 2 bronchial diverticula by one radiologist, but as grade 1 bronchial diverticula by the other.

FUTURE DIRECTIONS

To further investigate the importance of pulmonary chronic inflammation to lung cancer risk in smokers, we aim to assess he relationship between lung cancer, emphysema and airways disease by using high-precision 3D image analysis tools on volumetric thin-section CT data.

Low-dose thin-section CT emphysema and airways features of subjects with either symptomatic or MILD detected lung cancer will becompared with those of controls recruited by the same lung cancer screening trial. All CT scans will be obtained according to the same protocol and analyzed with a prototypical detection softwares (MeVis research).

Multiple regression models will be used to assess emphysema and airways features as potential risk factor for lung cancer, after allowance for gender, age, body mass index (BMI), smoking history, forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), and FEV_1/FVC ratio.

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