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Increased mean lung density: Another independent predictor of lung cancer?

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ABSTRACT

Objectives: To investigate the relationship between emphysema phenotype, mean lung density (MLD), lung function and lung cancer by using an automated multiple feature analysis tool on thin-section computed tomography (CT) data.
Methods: Both emphysema phenotype and MLD evaluated by automated quantitative CT analysis were compared between outpatients and screening participants with lung cancer ($n = 119$) and controls ($n = 989$). Emphysema phenotype was defined by assessing features such as extent, distribution on core/peel of the lung and hole size. Adjusted multiple logistic regression models were used to evaluate independent associations of CT densitometric measurements and pulmonary function test (PFT) with lung cancer risk.
Results: No emphysema feature was associated with lung cancer. Lung cancer risk increased with decreasing values of forced expiratory volume in 1 s (FEV_1) independently of MLD (OR 5.37, 95% CI: 2.63–10.97 for $FEV_1 < 60\%$ vs. $FEV_1 \geq 90\%$), and with increasing MLD independently of FEV_1 (OR 3.00, 95% CI: 1.60–5.63 for MLD > −823 vs. MLD < −857 Hounsfield units).
Conclusion: Emphysema per se was not associated with lung cancer whereas decreased FEV_1 was confirmed as being a strong and independent risk factor. The cross-sectional association between increased MLD and lung cancer requires future validations.

1. Introduction

The importance of refining the prediction of lung cancer is increasingly being recognized in the lung cancer screening debate. For a screening program to be beneficial and cost-effective, it is necessary to identify individuals at highest risk of cancer so that there is an adequate ratio of prevalence of the disease to the number of false-positive findings.[1] Simple data, such as mean lung density (MLD), a number of emphysema features as determined by low-dose computed tomography (LDCT), pulmonary function test (PFT) results, or a combination of the three might provide complementary information for lung cancer risk stratification either in screening or routine setting.

Several studies have shown that airflow obstruction is associated with a 4–6-fold increased risk of lung cancer independent of smoking history,[2–4] although it remains a matter of debate what component of airflow obstruction can contribute to this risk; in fact, some studies showed that the extent of emphysema is an independent risk factor for lung cancer,[5–7] while others did not.[2,8–10] In addition, two studies recently reported no association between automated CT measures of proximal (segmental and subsegmental) airway disease and lung cancer.[9,10]

However, previous studies did only include subjects with lung cancer detected in a screening setting and the emphysema

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phenotype as well as MLD were not fully assessed.[2,5,6,8–10] There is evidence that screening-detected lung cancers may differ from the general pool of lung cancers in their morphology, histology, and prognosis.[11,12] Likewise, emphysema in screening participants may be different from that of outpatients with lung cancer. The latest CT technical developments allow the automated characterization of emphysema based on spatial distribution and size of the emphysematous areas, thus further phenotyping the emphysema itself.[13] Furthermore, MLD as a more global index of pulmonary disease, might have an important predictive value.

In this study, we explored the relationship between emphysema phenotype, MLD, lung function and lung cancer by using an automated multiple features analysis tool on volumetric thin-section CT data.

2. Materials and methods

2.1. Study population

The Institutional Review Board of the YYYY approved the study and informed patient consent was obtained from all subjects.

Our study population consisted of 1108 individuals (age range 31–80 years, mean age 58.9 ± 6.7 years), 733 men (age range 31–80 years, mean age 57.7 ± 6.4 years) and 375 women (age range 32–79 years, mean age 59.6 ± 6.7 years). The lung cancer cases (119/1108, 10.7%) comprised two separate subgroups: 42/119 (35.3%) subjects with lung cancer consecutively detected by a lung cancer screening project, namely the XXXX trial, between April 2006 and June 2010, and 77/119 (64.7%) outpatients who underwent both PFT and CT scanning similar to what prescribed by the XXXX protocol for newly diagnosed lung cancer between January 2007 and August 2010. The cases of the screening group (age range 52–78 years, mean age 63.2 ± 6.5 years) consists of 34 men: age range 52–78 years, mean age 63.1 ± 6.7 years, and 8 women: age range 55–70 years, mean age 63.6 ± 6.0 years. The outpatients (age range 31–80 years, mean age 65.3 ± 10.2 years) include 61 men: age range 32–79 years, mean age 67.1 ± 8.7 years; and 16 women: age range 31–80 years, mean age 58.5 ± 12.8 years. We also decided to add to the study cohort to these outpatients as, in our opinion, this expanded study population would be more representative of the disease as a whole (owing to the inclusion of a higher proportion of tumors at advanced stages and with different histologies).

The controls (n = 989/1108, 89.2%: age range 49–78 years, mean age 58.3 ± 5.9 years; 638 men: 49–78 years, mean age 58.6 ± 5.9 years; 351 women: age range 49–75 years, mean age 57.6 ± 5.9 years) consisted of a subgroup of XXXX participants without lung cancer consecutively evaluated between September 2007 and September 2008. All the study subjects were recruited at the YYYY.

Details of XXXX eligibility criteria and PFT have been previously described.[14]

2.2. Low-dose CT

LDCT was performed by using 16-detector row CT scanner (Somatom Sensation 16, Siemens Medical Solutions, Forchheim, Germany). All LDCT scans of the whole lung were acquired during one deep inspiratory breath-hold without the use of the contrast medium. The scanner was calibrated on air daily to allow reliable measurements and comparison between examinations. Standard LDCT parameters were as follows: 120 kV, effective 30 mAs, individual detector collimation 0.75 mm, gantry rotation time 0.5 s, pitch 1.5, scan range from the lung bases to lung apices. The assessment of both emphysema and MLD was performed on LDCT images reconstructed as follows: 1-mm-thick sections with a reconstruction increment of 1 mm and a sharp kernel (medium-sharp kernel – B50f).

2.3. CT analysis

LDCT examinations were transferred to a separate PC workstation and analyzed for emphysema assessment by one operator (YY, with 8 years of experience in chest imaging) by using a prototypical software (Fraunhofer MEVIS, Bremen, Germany) that was informed about the lung cancer location within each pulmonary lobe. This software allows the application of high-precision 3D image analysis tools to volumetric CT data providing a fully automated lung segmentation (excluding larger solid lung nodules and masses) and assessment of the following CT parameters (Fig. 1): MLD, emphysema proportion (defined as the percentage of lung voxels below −950 HU), and distribution (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). 3D-connected emphysematous regions were further categorized according to their volumes. The emphysematous volumes were classified as following: 2–8 mm^3 (class 1); 8–65 mm^3 (class 2); 65–120 mm^3 (class 3); and >120 mm^3 (class 4), adapted from Blechschmidt et al. for 3-dimensional measurements.[15] In sharp kernel images, noise was further reduced by application of a 3 × 3 kernel-based axial Gauss smoothing. For each cluster class, the software reports the percentage of lung or lobe volume occupied by emphysematous clusters of that class. Semi-automated segmentation requires approximately 7 min per case.

The operator visually reviewed LDCT images to assess whether the lung cancers or associated atelectasis were automatically excluded by the segmentation process and indeed suitable for the densitometric analysis.

To establish whether the relationship between increased MLD and lung cancer might have been influenced by any other concomitant lung disease (e.g. interstitial lung disease, signs of infection or lymphangitis carcinomatosis etc.), two operators (YY and ZZ, with 8 and 3 years of experience in chest imaging, respectively) jointly reviewed the LDCT of all cases with a MLD higher than −823 HU (n = 35) in a second time (in a non pre-specified post hoc analysis). The interobserver agreement was not obtained. Observers were recommended to use the glossary of the Fleischner Society.[16] In addition, densitometric analysis was performed for those XXXX cases with baseline LDCT without lung cancer (7/35, 20%; mean time interval 2.2 years).

2.4. Data analysis

Cases (n = 119) and controls (n = 989) were compared according to selected demographic, functional and radiological variables, to test the differences of means of continuous variables by Student t test and differences of categorical variable distributions by (^{2} test.

To quantify the association between, FEV_1%, FEV_1/FVC, emphysema features, MLD as determined by automated CT analysis and lung cancer risk, we applied unconditional multivariate logistic regression equations to compute the odds ratios (OR) of lung cancer and the corresponding 95% confidence intervals (CI), using two sets of adjustment variables: (1) age, gender, smoking status, years of smoking, number of cigarettes per day and body mass index (BMI); (2) all the variables described in 1 plus reciprocal adjustment for whole-lung emphysema extent and FEV_1% and MLD as appropriate, to evaluate mutual independence. In accordance with previous studies, a cut-off of 90% predicted for FEV_1 and 70% for FEV_1/FVC ratio were adopted.[4,17] Since the effect of dose and duration of smoking is substantially different in the