CHEST

Assessing the Relationship Between Lung Cancer Risk and Emphysema Detected on Low-Dose CT of the Chest*

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Rationale: Identification of risk factors for lung cancer can help in selecting patients who may benefit the most from smoking cessation interventions, early detection, or chemoprevention.

Objective: To evaluate whether the presence of emphysema on low-radiation-dose CT (LDCT) of the chest is an independent risk factor for lung cancer.

Methods: The study used data from a prospective cohort of 1,166 former and current smokers participating in a lung cancer screening study. All individuals underwent a baseline LDCT and spirometry followed by yearly repeat LDCT studies. The incidence density of lung cancer among patients with and without emphysema on LDCT was estimated. Stratified and multiple regression analyses were used to assess whether emphysema is an independent risk factor for lung cancer after adjusting for age, gender, smoking history, and the presence of airway obstruction on spirometry.

Results: On univariate analysis, the incidence density of lung cancer among individuals with and without emphysema on LDCT was 25.0 per 1,000 person-years and 7.5 per 1,000 person-years, respectively (risk ratio [RR], 3.33; 95% confidence interval [CI], 1.41 to 7.85). Emphysema was also associated with increased risk of lung cancer when the analysis was limited to individuals without airway obstruction on spirometry (RR, 4.33; 95% CI, 1.04 to 18.16). Multivariate analysis showed that the presence of emphysema (RR, 2.51; 95% CI, 1.01 to 6.23) on LDCT but not airway obstruction (RR, 2.10; 95% CI, 0.79 to 5.58) was associated with increased risk of lung cancer after adjusting for potential cofounders.

Conclusions: Results suggest that the presence of emphysema on LDCT is an independent risk factor for lung cancer.   *(CHEST 2007; 132:1932–1938)*

Key words: airway obstruction; CT; emphysema; lung cancer; risk factors

Abbreviations: CI = confidence interval; IQR = interquartile range; LDCT = low-radiation-dose CT; RR = risk ratio

Lung cancer is the deadliest malignancy in the world among men and women.[1,2] Major public health efforts have focused on developing new interventions to decrease smoking rates, the main risk factor for lung cancer, and to test for strategies that could lead to early detection or effective chemoprevention. In particular, lung cancer screening using low-radiation-dose CT (LDCT) is a promising strategy currently undergoing intensive research efforts. An important aspect of these strategies is the ability to identify patients at high risk for lung cancer who may benefit the most from smoking

cessation treatments, early diagnosis, or chemoprevention. Moreover, several studies[3] have shown that the cost-effectiveness of these interventions is highly dependent on the prevalence of lung cancer in the target population.

COPD, also strongly associated with cigarette smoking, is a highly prevalent condition that in industrialized countries is only second to heart disease as a cause of death.[3] Most patients with COPD have a combination of chronic bronchitis and emphysema, which is anatomically defined as an abnormal permanent enlargement of the airspaces distal to

the terminal bronchioles, accompanied by destruction of their walls without obvious fibrosis.[4] According to international guidelines, the diagnosis of COPD requires the presence of airway obstruction on spirometry.[5] In recent years, CT has been shown to accurately identify areas of the lung parenchyma involved with emphysema.[5,6] CT may be more sensitive than pulmonary function tests for the detection of emphysema, but the clinical significance of emphysema diagnosed on CT in the absence of airway obstruction is not yet clear.

It has been shown that patients with COPD, defined by the presence of airway obstruction, are at increased risk for lung cancer.[7] However, there are limited data regarding the potential association between emphysema diagnosed on chest CT and lung cancer, particularly among individuals with normal airway function. In this study, we used data from an unselected population of current and former smokers participating in a lung cancer screening study to assess whether emphysema detected on LDCT is an independent risk factor for lung cancer.

MATERIALS AND METHODS

The study was conducted using data from a prospective cohort of individuals enrolled in a lung cancer screening study using LDCT from September 2000 to December 2005.[8] Eligibility criteria included age $\geq$ 40 years, > 10 pack-year smoking history, and no symptoms of lung cancer. The study protocol consisted of a baseline LDCT of the chest followed by annual repeat studies for up to 5 years. All patients underwent spirometry at enrollment and a baseline standardized questionnaire to collect sociodemographic information and smoking history data. The ethics committee of the University of Navarra approved the study protocol, and all subjects signed an informed consent form prior to participation.

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LDCT

LDCT examinations were performed in a single breath-hold at end-inspiration. The initial 297 subjects were studied with a single-slice helical scanner (Somatom Plus 4; Siemens; Erlangen, Germany) at low-dose settings (140 kilovolt peak, 43 mA seconds) and 1.5 pitch with a collimation of 8 mm. We used a four-row multislice helical CT scanner (Somatom Volume Zoom; Siemens; Forchheim, Germany) also at a low-dose setting (120 kilovolt peak, 20 mA seconds, and 1.25-mm slice thickness) for all subsequent studies. All images were reconstructed using a high-spatial-frequency algorithm and displayed at window settings appropriate for viewing the lung parenchyma (window width of 1,500 Hounsfield units, and window center of − 650 Hounsfield units).[9]

Assessment of Emphysema on LDCT

All images were read by two expert chest radiologists for visual assessment of the presence of emphysema, using validated criteria.[6] In brief, the extent of emphysema was graded from 0 to 4, with a grade of 0 indicating no emphysema, and a grade of 4 indicating the presence of emphysema in > 75% of the lung.[6] For the purpose of this study, patients with a score $\geq$ 1 were classified as having emphysema.

Spirometry

Airway function was measured at baseline in all study participants using a flow spirometer (Vmax 22; SensorMedics; Yorba Linda, CA) according to the standards of the American Thoracic Society.[4] FEV_1 and FVC measures were expressed as a percentage of the predicted value according to the European Community Lung Health Survey.[10] Using the criteria established by the Global Initiative for Chronic Obstructive Lung Disease, subjects with a FEV_1/FVC ratio < 70% were classified as having airway obstruction.[5]

Lung Cancer Diagnostic Algorithm

Study participants were evaluated for the presence of lung cancer using a standardized diagnostic algorithm.[11] Briefly, patients with noncalcified nodules < 10 mm were followed up with repeat LDCTs and further workup if growth of a nodule was detected. Subjects with suspicious nodules $\geq$ 10 mm were immediately referred for positron emission tomography, percutaneous needle biopsy, or intraoperative biopsy. For the purpose of the study, all cases of lung cancer diagnosed as a consequence of screening or due to a new onset of symptoms (interval cases) were included in the analysis.

Data Analysis

Normal data are presented as mean $\pm$ SD, and nonnormal variables are presented as median (interquartile range [IQR]). The agreement between raters for the visual assessment of emphysema and the κ coefficient for interrater reliability was calculated.[12,13]

The incidence density of lung cancer was calculated with person-years as the denominator under the Poisson assumption.[14] We used the risk ratio (RR) with 95% confidence intervals (CIs) to compare the risk of lung cancer among study subjects with and without emphysema.

Stratified analyses were also conducted to evaluate the relationship between emphysema and lung cancer risk among patients with normal airway function. We used Poisson regression

Table 1—*Baseline Characteristics of Study Participants**

Characteristics	Data
Age, yr	54 ± 8
Male gender, %	74
Smoking history, median pack-yr	33 (IQR: 22)
Spirometry results, % predicted	
FEV_1	95 ± 18
FVC	105 ± 16
FEV_1/FVC ratio	75 ± 8
Airway obstruction, %†	25
LDCT result	
Emphysema, %‡	29

*Data are presented as mean ± SD unless otherwise indicated.
†Percentage of participants with FEV_1/FVC < 70% of predicted.
‡Percentage of participants with emphysema on LDCT grade 1 or more.

to assess whether emphysema on LDCT was independently associated with lung cancer incidence density after controlling for other known risk factors such as age, gender, presence of airway obstruction, and smoking history (number of pack-years). All analyses were performed with statistical software (version 9.0; SAS Institute; Cary, NC) and using two-sided p values.

Results

A total of 1,166 individuals were included in the study. Baseline characteristics of the study participants are shown in Table 1. All participants were white western Europeans, mean age was 54 ± 8 years, and 74% were male. The median number of pack-years smoked was 33 (IQR: 22 pack-years). Overall, 29% (95% CI, 26 to 31%) of the subjects had emphysema on baseline LDCT and 25% (95% CI, 22 to 27%) had airway obstruction on spirometry (Fig 1). Fifty-three percent of the participants with emphysema on CT had no airway obstruction. The interrater agreement for the presence or absence of emphysema based on visual assessment was excellent (κ coefficient = 0.91).

Lung cancer was diagnosed in 23 participants. Seventeen cases were detected on baseline screening, and 6 cases were detected on annual repeat screening. No interval lung cancers were diagnosed. Adenocarcinoma was the most frequent histologic type (57%), followed by squamous cell carcinoma (22%), small cell carcinoma (17%), and large cell carcinoma (4%). Nearly 80% of the cancers were diagnosed in stage I, 13% in stage II, and 7% in stage III.

Relationship Between Emphysema Distribution, Cancer Location, and Histologic Type

Of the 17 individuals with lung cancer and emphysema on LDCT, 16 patients (94%) had heterogenous emphysema with upper-lobe predominance and the cancer was located in the upper lobes. One individual had homogenous emphysema and lung cancer in the left lower lobe. The histologic type of cancer in 10 of the 17 individuals with emphysema (58%) was adenocarcinoma.
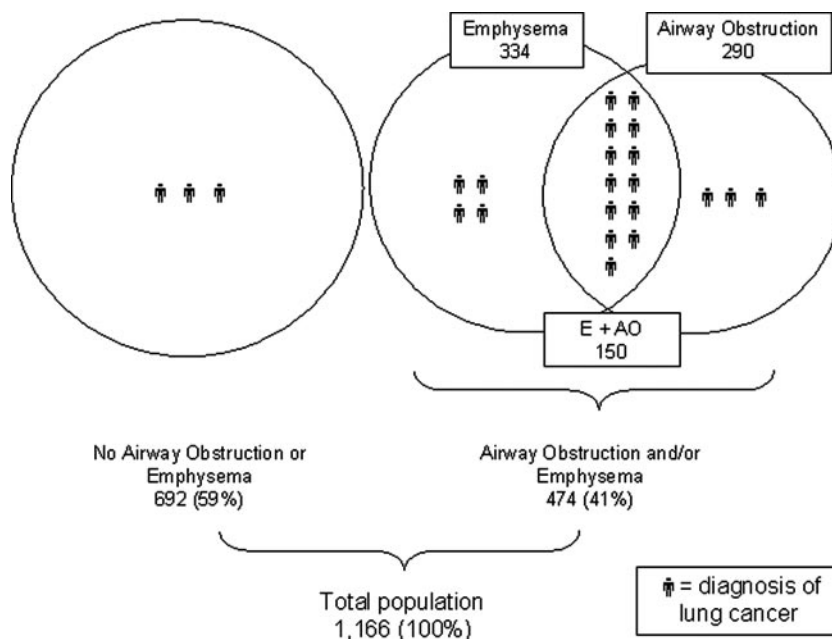

FIGURE 1. Distribution of participants with lung cancer according to the presence or absence of airway obstruction (AO) and/or emphysema (E).

Table 2—Unadjusted and Stratified Association Between Emphysema, Airway Obstruction, and Incidence of Lung Cancer

Risk Factors	No. of Lung Cancers	Person-Years of Follow-up	Incidence Density (per 1,000 Person-Years)	RR (95% CI)
Univariate analysis				
No emphysema	8	1,065	7.5	Reference
Emphysema	15	600	25.0	3.33 (1.41–7.85)
No airway obstruction	8	1,200	6.7	Reference
Airway obstruction	15	465	32.3	4.83 (2.05–11.41)
No emphysema, no airway obstruction	3	876	3.4	Reference
Emphysema or airway obstruction	10	531	18.8	5.50 (1.51–19.99)
Emphysema and airway obstruction	10	267	37.5	10.94 (3.01–39.74)
Stratified analysis				
No airway obstruction				
No emphysema	3	876	3.5	Reference
Emphysema	5	333	15.0	4.33 (1.04–18.16)
Airway obstruction				
No emphysema	5	198	2.5	Reference
Emphysema	10	267	3.8	1.48 (0.51–4.34)

Relationship Between Emphysema and the Risk of Lung Cancer

On univariate analysis, the incidence density of lung cancer among individuals with and without emphysema on LDCT was 25.0 per 1,000 person-years and 7.5 per 1,000 person-years, respectively (RR, 3.33; 95% CI, 1.41 to 7.85; Table 2). Similarly, the incidence density of lung cancer in individuals with and without airway obstruction on spirometry was 32.3 per 1,000 person-years and 6.7 per 1,000 person-years, respectively (RR, 4.83; 95% CI, 2.05 to 11.41).

A potential synergy between emphysema detected on LDCT and airway obstruction detected on spirometry is suggested by the increased incidence density of lung cancer in subjects with both conditions (37.5 per 1,000 person-years) as compared to those with neither one (3.4 per 1,000 person-years; RR, 5.49; 95% CI, 1.51 to 19.98). The incidence density of lung cancer in subjects with only one of the two abnormalities (emphysema or airway obstruction) was 18.8 per 1,000 person-years (RR, 10.94; 95% CI, 3.01 to 39.74; Table 2).

In the stratified analysis, the presence of emphysema on LDCT was associated with an increased likelihood of a lung cancer diagnosis among subjects without airway obstruction (RR, 4.33; 95% CI, 1.04 to 18.16). When the analysis was limited to participants with airway obstruction on spirometry, no relationship between emphysema on LDCT and lung cancer risk was found (RR, 1.48; 95% CI, 0.51 to 4.34).

The results of the Poisson regression analyses are shown in Table 3. Emphysema detected on LDCT was significantly associated with a higher risk of lung cancer in a model adjusting for age, gender, and number of pack-years of smoking (RR, 3.13; 95% CI, 1.32 to 7.44; model 1). Lung cancer was also more common among patients with airway obstruction after controlling for the same covariates (RR, 2.89; 95% CI, 1.14 to 7.27; model 2). However, in a final model (model 3) that included terms for presence of emphysema, airway obstruction, age, gender, and smoking history, emphysema (RR, 2.51; 95% CI, 1.01 to 6.23) and the number of pack-years of smoking (RR, 2.9; 95% CI, 1.1 to 7.2) but not airway obstruction (RR, 2.10; 95% CI, 0.79 to 5.58) were independently associated with a higher risk for lung cancer.

DISCUSSION

Results of this prospective cohort study of current and former smokers suggest that the presence of

Table 3—Results of Multivariate Analysis*

Risk Factors	RR	95% CI
Model 1		
Emphysema	3.13	1.32–7.44
No emphysema	Reference	
Model 2		
Airway obstruction	2.89	1.14–7.27
No airway obstruction	Reference	
Model 3		
Emphysema	2.51	1.01–6.23
No emphysema	Reference	
Airway obstruction	2.10	0.79–5.58
No airway obstruction	Reference	

*All models were adjusted for age, gender, and No. of pack-years of smoking. Pack-years of smoking was significantly associated with an increased risk of lung cancer in all three models.

emphysema on LDCT is associated with an increased risk for lung cancer. Stratified and multivariate analyses showed that this association was significant even after controlling for the presence of airway obstruction on spirometry, suggesting that emphysema on LDCT is an independent risk factor for lung cancer. This information can help identify patients at high risk for lung cancer who may benefit from more-aggressive preventive interventions or lung cancer screening programs.

The majority of lung cancers occur in current or former smokers, and the risk increases with older age and longer exposure to tobacco.[3] However, lung cancer develops in only a minority of smokers. Therefore, the identification of additional factors that may help in the selection of individuals with the highest risk may be useful. Many reports[7] have linked abnormal airway function on pulmonary function testing with an increased risk for lung cancer. There is less information regarding the association between emphysema and lung cancer.[15–17]

Emphysema has traditionally been a pathologic diagnosis, but the development of CT-based image analysis techniques has lead to accurate noninvasive *in vivo* detection and quantification of emphysema.[18] For example, CT has been shown to be useful in the selection of individuals with severe emphysema who are at a greater risk for a poor outcome after lung volume reduction surgery (*ie*, those with a homogenous distribution of emphysema).[6] Moreover, quantification of emphysema using CT has been used to follow the effects of replacement therapy in patients with α_1-antitrypsin deficiency.[19,20] However, the clinical significance of emphysema on CT among individuals without symptoms or with normal pulmonary function tests remains unclear. A novelty of this study is the use of LDCT instead of high-resolution CT, as has been used in the aforementioned studies.

In this study, a strong association between emphysema detected on LDCT and lung cancer risk was found even among individuals with normal airway function. These results are consistent with previous retrospective and epidemiologic reports.[15–17,21] Additionally, a recent study[22] has found that emphysema detected on CT, and not airway obstruction, was associated with a worse prognosis in smokers with early stage lung cancer. Conversely, a case-controlled study[23] using data from subjects enrolled in the Mayo Clinic LDCT early lung cancer detection study found that severe airway obstruction, but not emphysema, was associated with a higher risk of lung cancer. The discrepancy in the results between this study and ours may be explained by several reasons. Firstly, the Mayo Clinic study follows a case-control design in which only a small subgroup of individuals of the entire cohort is used in the analysis. In our study, the entire population entered into the lung cancer screening trial was included in the analysis. Secondly, the proportion of subjects with airway obstruction that were included in the analysis was 67% and 79% in the control and lung cancer groups, respectively, in the Mayo Clinic study, and 25% in ours. Lastly, the method to determine the presence of emphysema was quantitative in the Mayo Clinic study and by visual assessment in ours. In the former, participants were subclassified into groups depending on the amount of emphysema; whereas in our study, only the presence or absence of emphysema was considered for the analysis.

The findings presented herein have several potential clinical implications. Lung cancer is the most lethal cancer in the world mainly due to the fact that > 80% of cases are diagnosed in advanced stages of the disease. In the last few years, a great interest in lung cancer screening research has emerged. A recent report by the International Early Lung Cancer Action Program consortium,[11] among other studies, has shown promising results using annual LDCT. Other studies[24] have found different results raising questions about mortality benefit, cost-effectiveness, and safety of lung cancer screening using LDCT. Several randomized control studies in the United States and in Europe are underway, and results should be available in a few years. If early detection of lung cancer with LDCT is shown to be effective by studies currently underway, the appropriate selection of the target population will be very important. For a screening program to be beneficial and cost-effective, it is necessary to identify individuals with the highest risk for lung cancer so that there is an adequate ratio of prevalence of the disease to the number of false-positive findings. The results presented herein suggest that emphysema detected on a baseline LDCT could be used in this context to identify individuals who may need additional follow-up studies. Conversely, individuals with no evidence of emphysema and with no suspicious nodules on a baseline LDCT may not require further screening. Additionally, LDCT screening may provide a means for diagnosing emphysema at an earlier stage, even before abnormalities develop that are detectable on pulmonary function testing. Whether the detection of emphysema in such early stages will have an impact on outcomes or on the natural history of the disease by earlier interventions is a question that should be explored in future studies. As an example, this information could be used to identify individuals who may need more-aggressive smoking cessation interventions. Smoking cessation has been shown to reduce the risk of lung cancer as well as to reduce the rate of progression of COPD.[25,26]

Several mechanisms have been proposed to explain the link between lung cancer and COPD.[27] Firstly, both diseases share tobacco smoking as the

most important etiologic factor. However, the majority of smokers remain disease-free throughout their lives, and only a few have airway obstruction, emphysema, and/or lung cancer. Smoke contains high concentrations of reactive oxygen species together with thousands of particles that are potentially carcinogenic and may induce inflammation in all smokers.[28] However, it remains unclear why there are different responses to tobacco with some individuals having the hallmarks of cancer (uncontrolled cell proliferation, lack of cellular apoptosis, tissue invasion, and angiogenesis), others the hallmarks of COPD (increased apoptosis, matrix degeneration, ineffective tissue repair, inflammation, and lack of angiogenesis), while the majority remain disease free.[27]

A limitation of this study is the relatively small number of cancers diagnosed among the study participants. This is expected given the prospective design and the relatively low incidence of lung cancer even among high-risk smokers. However, the number of cases and the prevalence of emphysema and airway obstruction in the study population were sufficiently large to obtain positive findings even after using stratified analysis. Another potential limitation is that emphysema on LDCT was only determined qualitatively. However, it has been shown that qualitative assessment is a valid and reliable tool for the characterization of emphysema on CT.[6] Furthermore, the prevalence of emphysema based on qualitative measurements in this study population is similar to what has been reported in other series of high-risk individuals.[29] Lastly, we lacked complete information about current smoking status of some study participants. Thus, we were not able to adjust for the potential influence of smoking status (current vs former) on the risk of lung cancer in the multivariate analyses.

In summary, the results of this study suggest that emphysema detected on LDCT is an independent risk factor for lung cancer. If confirmed, this information can be used to select candidates for lung cancer screening or chemoprevention trials.

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