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The correlation of emphysema or airway obstruction with the risk of lung cancer: a matched case-controlled study

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ABSTRACT: A matched case-controlled study was conducted to determine if airway obstruction or emphysema were associated with an increased risk of lung cancer.

Lung cancer cases (n=24) were identified through a low-dose spiral computed tomography (CT) screening trial from 1,520 participants. Four controls without lung cancer were selected for each case from the participants and matched by sex, age and smoking history. Emphysema was assessed by quantitative CT analysis. Conditional logistic regression was employed to assess results of spirometry and CT quantitative analysis as potential risk factors for lung cancer.

The likelihood of lung cancer was found to be significantly increased for those with forced expiratory volume in one second (FEV_1) $\leqslant$40% of predicted. The results suggested that a lower percentage of predicted FEV_1 was indicative of lung cancer. No compelling evidence was found to suggest that the percentage of emphysema was associated with lung cancer.

These results suggest an increased risk of lung cancer associated with airway obstruction. However, percentage of emphysema as determined by computed tomography was not associated with an increased risk of lung cancer.

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Lung cancer is the number one cause of death from cancer in the USA [1]. Approximately 85% of lung cancer occurs in current or former smokers. The risk of lung cancer increases with age and amount of smoke exposure [2]. Chronic obstructive pulmonary disease (COPD) is defined as a disease state characterized by the presence of airflow obstruction due to chronic bronchitis or emphysema [3]. Overall, smoking accounts for an estimated 80–90% of the risk of developing COPD [4]. Lung cancers frequently occur in patients with COPD [5]. Although cigarette smoke is the common aetiological factor for both lung cancer and COPD, several studies have shown that airway obstruction is associated with a four- to six-fold increased risk of lung cancer independent of smoking history [6, 7].

Emphysema is defined anatomically as abnormal permanent enlargement of the airspaces distal to the terminal bronchioles, accompanied by destruction of their walls without obvious fibrosis [3]. Recent studies have reported the detection of asymptomatic lung cancers in 2–5% of patients with severe emphysema who were being evaluated for lung volume reduction surgery [8, 9]. These lung cancers were located peripherally in the lung and detected by computed tomography (CT) scans of the chest, which were performed as part of the pre-operative evaluation. Nevertheless, the relationship between the degree of emphysema, as measured by CT, and the risk of lung cancer has not been clearly defined.

Because the definition of emphysema is based on the anatomical demonstration of destruction of lung tissue, CT is well suited for *in vivo* identification [10]. CT and particularly, high-resolution CT (HRCT) detects emphysema with a greater sensitivity than chest radiography or pulmonary-function tests. In addition to being evaluated visually, emphysematous changes on CT can be quantified objectively by measuring lung attenuation [11, 12]. Lung attenuation values in normal subjects range from -770–-875 Hounsfield units (HU) [13]. The density in emphysematous lung is low, and voxels with low attenuation values can be highlighted by the use of "density mask" software [11]. Quantitative CT analysis using the "density-mask" technique has been shown to correlate well with the pathological assessment of emphysema. Recently, this technique has been applied to three dimensional (3D) volumetric reconstructions from spiral CT scans to assess lung volume and quantitation of emphysema [14, 15].

In 1999, investigators at Mayo Clinic launched an early lung cancer screening trial using low-dose spiral CT scan supplemented by sputum cytology and spirometry [16]. Using the data acquired from this trial, a matched case-controlled study was performed to determine if airways obstruction measured by

spirometry or emphysema assessed by quantitative CT were associated with an increased risk of lung cancer in the screened cohort.

Materials and methods

Study subjects

From January 1–December 31 1999, 1,520 participants (52% males) were entered into the low-dose spiral CT screening trial for detecting lung cancer at Mayo Clinic, Rochester. Males and females, aged $\geqslant$50 yrs with a life expectancy of at least 5 yrs, who were current or former smokers (having quit <10 yrs previously) of $\geqslant$20 pack-yrs, and who did not use supplemental oxygen were recruited. Candidates with a history of cancer within 5 yrs other than nonmelanoma skin cancer, *in situ* cervical cancer, or localized prostate cancer were excluded. The participants were recruited from respondents to advertisements and articles published in the lay press and from television reports.

The study protocol was approved by the Institutional Review Board and written informed consent was obtained. Initial studies included a low-dose spiral CT scan of the chest, induced sputum cytology and spirometry (prevalence screening). By protocol, all participants will be retested yearly for 3 yrs (incidence screening). This report is based on cases of lung cancer detected by January 5 2001 after 1 yr of follow-up.

Among 1,520 participants, 24 cases have been diagnosed with lung cancer to date. Of 24 cases 22 were detected by prevalence screening and two cases were detected by incidence screening. The controls were selected from participants without lung cancer. A 1:4 matched set design was employed whereby each lung cancer case was matched to four controls. Matching variables included sex, age, and pack-yrs of smoking with optimal matched sets identified using the approach described by ROSENBAUM [17] and BERGSTRALH and KOSANKE [18].

Computed tomography scan

CT scans were performed with a High Speed Advantage CT scanner (General Electric Medical Systems, Milwaukee, WI, USA) in the helical mode without contrast material. The technical scan parameters included the following: 120 kilovolt peak (kVp), 40 milliamperes (mA), 5 mm collimation with 3.5 mm reconstruction interval, 30 $mm \cdot s^{-1}$ table speed and 2:1 pitch. The CT images of the entire lung region were obtained in a single breath hold at full inspiration. Lung images were reconstructed with a high-frequency, edge-enhancing algorithm.

Quantitative computed tomography analysis

The 3D images of the lungs were reconstructed with the Advantage Windows 3D Analysis Package (General Electric Medical Systems). The threshold limits of -700–-1,024 HU were applied to exclude soft tissue surrounding the lung and large vessels within the lung. The 3D images were viewed as a shaded surface display at multiple angles to ensure the model was valid (fig. 1). The trachea, main-stem bronchi, and gastrointestinal structures were selectively removed from the model.

A histogram display of the 3D images showed the volume, attenuation distribution and SD of attenuation. The histogram provided a frequency distribution of voxels with specific attenuation numbers (in HU) in the lung. The volume of voxels with attenuation values <-900 HU were measured on the histogram. The -900 HU value was a threshold previously reported to separate emphysematous lung from normal lung [10, 15]. The volume of low attenuation voxels was then divided by the total lung volume to obtain the percentage of emphysema.

Spirometry

Spirometry was performed with a Puritan Bennett Renaissance pneumotach-based flow spirometer (Mallinckrodt, St Louis, MO, USA) according to the standards of the American Thoracic Society [19]. Forced expiratory volume in one second (FEV_1) was expressed as % of predicted using the reference equations of CRAPO *et al.* [20].

Statistical analysis

All analyses were performed using, the 1:4 matched set of 24 cases and 96 controls. Conditional logistic regression was employed to assess whether % pred FEV_1, the ratio of FEV_1 to forced vital capacity (FEV_1/FVC), or the percentage of emphysema, as determined by the quantitative CT analysis are risk factors for lung cancer [21]. Since cases and controls

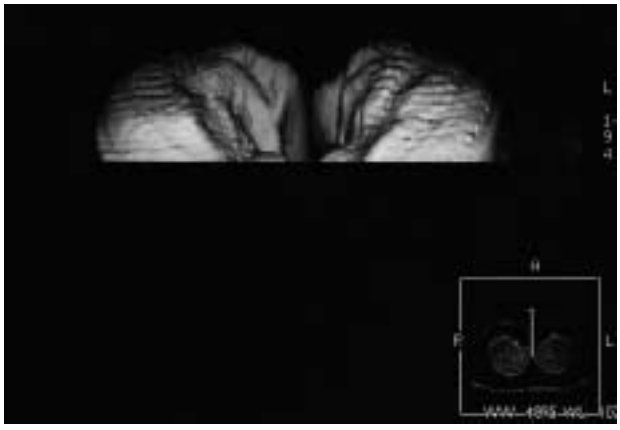

Fig. 1. – Volume reconstruction of the upper one-third of the lung. Axial images were constructed using three-dimensional volume rendering. From the volume reconstruction, the computer can calculate total lung volume or volume of an emphysematous lung. The trachea has been deliberately excluded from the reconstruction. The major airways to the segmental bronchi have been excluded as the computer cannot distinguish between normal dead space air and emphysematous lung.

were matched for age, sex, and pack-yrs of smoking history, the use of the conditional logistic regression adjusts for these variables. Neither current-smoking status nor length of abstinence from smoking were considered in the matching procedure. Therefore, the duration of abstinence from smoking was calculated for each individual and included as a covariate in the conditional logistic regression analysis. For current smokers the duration of abstinence from smoking was assigned a value of zero. Per cent pred FEV_1 was analysed as a continuous variable and also as a categorical variable using the categories $\geqslant 81\%$, 61–80%, 41–60%, and $\leqslant 40\%$ [22]. FEV_1/FVC was analysed as a continuous variable and also as a categorical variable using the categories $\geqslant 71\%$, 61–70%, 51–60%, and $\leqslant 50\%$. Percentage of emphysema, as determined by the quantitative CT analysis, was analysed as a continuous variable and also as a categorical variable using the categories 0–4%, 5–9%, 10–14%, and $\geqslant 15\%$. Odds ratios (OR) with corresponding 95% confidence intervals (Cl) were calculated where appropriate. In all cases, two-sided tests were used with $p \leqslant 0.05$ considered statistically significant.

Results

There were 24 cases (10 males, 14 females) and 96 controls (40 males, 56 females) (table 1). Cases and controls were matched (1:4) for sex, age, and pack-yrs of smoking history. The mean±SD age was 63.7± 6.9 yrs for the cases and 63.2±6.3 yrs for the controls. Age was matched within ±3 yrs of the case for 97% (93 of 96) of the controls. The mean smoking history was 59±15 pack-yrs for cases and 58±14 pack-yrs for controls. Pack-yrs of smoking history were matched within ±5 pack-yrs of the case for 90% (86 of 96) of the controls and within ±10 pack-yrs of the case for 97% (93 of 96) of the controls. Eleven of 24 (46%) cases and 55 of 96 (57%) controls were current smokers; and four of 24 (17%) cases and 14 of 96 (15%) controls had abstained from smoking for >5 yrs.

The cell types of the 24 lung cancer cases included small cell carcinoma in three, squamous cell carcinoma in six, adenocarcinoma in 14 (including two with bronchoalveolar carcinoma), and large cell carcinoma in one. There were 12 cancers each in the right and left lung. Ten of 24 (42%) lung cancers occurred in the upper lobes, one in the middle lobe, 12 (50%) in the lower lobes and one in both middle and lower lobes. Of the 21 nonsmall cell lung cancer cases, 14 (67%) were stage I, five (24%) were stage II, and two (10%) were stage IIIA at the time of diagnosis. All three small cell lung cancers were limited stage disease.

Conditional logistic regression was employed to assess results of spirometry and CT quantitative analysis as potential risk factors for lung cancer. The findings of these analyses are presented in table 2. When analysed as a continuous variable, the results suggested that a lower percentage of FEV_1 % pred was predictive of lung cancer (OR=1.2, for each 10% point decline, 95% confidence interval (CI) 1.0–1.5, p=0.082). When treated as a categorical variable, the likelihood of lung cancer was significantly increased for those with $FEV_1 \leqslant 40\%$ pred (OR=9.6, 95% CI 1.5–60.1 relative to those with $FEV_1 > 80\%$ pred, p=0.016). There was also evidence that suggested lower FEV_1/FVC was predictive of lung cancer (p=0.083) and that those with $FEV_1/FVC \leqslant 50\%$ pred were at increased risk (OR=4.1, 95% CI 1.0–17.2 relative to those with $FEV_1/FVC > 70\%$ pred, p=0.056). No evidence was found to suggest that the percentage of emphysema, as determined by the quantitative CT analysis, was associated with lung cancer (OR=1.1, for each 10% point increase, 95% CI 0.6–1.9, p=0.763).

Table 1. – Patient demographics[#]

	Controls	Cases
Subjects n	96	24
Gender %		
Female	58	58
Male	42	42
Age yrs		
Mean±SD	63.2±6.3	63.7±6.9
Range	54.0–79.0	55.0–79.0
Pack-yrs of smoking		
Mean±SD	57.8±14.4	59.0±15.2
Range	35.0–104.0	36.0–100.0
Smoking Status %		
Current	57	46
Former <5 yrs	28	37
Former ⩾5 yrs	15	17
Duration of abstinence[¶] yrs		
Mean±SD	1.5±2.6	1.9±2.9
Range	0–9.4	0–8.6

[#]: cases and controls were matched 1:4 for sex age and pack-yrs; [¶]: duration of abstinence from smoking was assigned a value of zero for current smokers.

Discussion

The results of this study indicate an increased risk of lung cancer associated with airway obstruction independent of smoking history. There was evidence suggesting that both lower percentage of FEV_1 % pred (OR=1.2, 95% CI 1.0–-1.5) and FEV_1/FVC (OR=1.4, 95% CI 1.0–2.2) were predictive of lung cancer. The authors found that severe airway obstruction, with an $FEV_1 \leqslant 40\%$ pred, was significantly associated with a markedly increased risk of lung cancer (OR=9.6, 95% CI 1.5–60.1). These data are consistent with previous prospective studies that assessed the risk of lung cancer in patients with airway obstruction [6, 7]. SKILLRUD *et al.* [6] studied 113 subjects with an FEV_1 of $\leqslant 70\%$ pred (mean FEV_1=45.8% pred) and 113 control subjects with an FEV_1 of >85%. All subjects were followed from 1973–1974 to 1984. Lung cancer developed in nine subjects and two control subjects. Subjects with COPD had a four-times greater risk of developing lung cancer than those without airway obstruction when matched for age, sex, occupation, and smoking history. Similarly, TOCKMAN *et al.* [7] demonstrated the risk of lung cancer in patients with

Table 2. – Conditional logistic regression results

	Controls	Cases	OR	95% CI	p-value
Subjects n	96	24			
Spirometry					
FEV1 % pred	75.6±17.6	67.5±24.4	1.2	1.0–1.5	0.082
⩾81	42 (43.8)	8 (33.3)	1.0		
61–80	34 (35.4)	7 (29.2)	1.1	0.3–3.9	>0.10
41–60	17 (17.7)	4 (16.7)	1.2	0.3–4.7	>0.10
⩽40	3 (3.1)	5 (20.8)	9.6	1.5–60.1	0.016
FEV1/FVC×100%	64.4±10.2	59.9±14.3	1.4	1.0–2.2	0.083
⩾71	32 (33.3)	5 (20.8)	1.0		
61–70	35 (36.5)	8 (33.3)	1.6	0.5–5.6	>0.10
51–60	17 (17.7)	4 (16.7)	1.7	0.4–7.4	>0.10
⩽50	12 (12.5)	7 (29.2)	4.1	1.0–17.2	0.056
Quantitative CT analysis					
Emphysema %	9.9±8.6	10.6±8.2	1.1	0.6–1.9	>0.10
<5	36 (37.5)	9 (37.5)	1.0		
5–9	18 (18.8)	1 (4.2)	0.2	0.0–2.0	>0.10
10–14	19 (19.8)	7 (29.2)	1.5	0.5–4.8	>0.10
⩾15	23 (24.0)	7 (29.2)	1.1	0.4–3.7	>0.10

Data are presented as n (%) or mean±SD unless otherwise stated. OR: odds ratio; CI: confidence interval; FEV1: forced expiratory volume in one second; FVC: forced vital capacity; CT: computed tomography.

moderate to severe airway obstruction from the Intermittent Positive Pressure Breathing Trial (n=676) and in participants with no obstruction to moderate obstruction in the Johns Hopkins Lung Project (n=3,728). A total of 22 participants died of lung cancer in the Intermittent Positive Pressure Breathing Trial and 19 in the Johns Hopkins Lung Project. Patients with airway obstruction defined as an FEV1 of <60% pred had a six-fold increased risk of lung cancer compared with those without airway obstruction. The risk of lung cancer increased with the severity of airway obstruction. Further evidence of the risk of lung cancer among those with airway obstruction was reported in the results of the Lung Health Study [23]. Among nearly 6,000 smokers with mild-to-moderate airway obstruction, lung cancer was the most common cause of death at the end of the 5 yrs of follow-up.

The current study suggests that percentage of emphysema, as assessed by quantitative CT, is not associated with an increased risk of lung cancer after adjustment for sex, age and smoking history. The discrepancy in lung cancer risk between airway obstruction and percentage of emphysema in this study is consistent with the observation by GELB *et al.* [24] that emphysema does not appear to be primarily responsible for airway obstruction in COPD. GELB *et al.* [24] found a fair to weak correlation between FEV1 % pred and either CT or morphologically scored emphysema. Similar observations were noted by GOULD *et al.* [25] and KUWANO *et al.* [26]. The discrepancy with previous reports [27, 28] which suggest that emphysema was primarily responsible for airway obstruction in COPD, may in part be related to limited availability of autopsy specimens of lobes or lungs [24].

Methodological limitations may provide another potential explanation for the results of this study. The percentage of emphysema was analysed by quantitative CT measurements of lung density using low-dose spiral CT. Quantitative CT with a standard-dose setting (140–200 mA) accurately reflects macroscopic emphysema [11]. Although reduction of the milliamperage increases the image noise, NAIDICH *et al.* [29] found that visualization of parenchymal structure was not affected by decreasing the milliamperage. ZWIREWICH *et al.* [30] showed that the low-dose and the standard-dose HRCT scans were equivalent in the evaluation of anatomical information as well as interstitial and air-space abnormalities. A recent study reported that low-dose spiral CT was equivalent to the standard-dose spiral CT at visualizing lung abnormalities [31]. Nevertheless, few studies have assessed emphysema by quantitating areas of low attenuation on low-dose spiral CT.

Another possible methodological limitation is the use of the lower attenuation threshold of -900 HU to identify emphysema in this study. The lower attenuation thresholds that have been used most widely are -900 or -910 HU on conventional 7- to 10-mm collimation CT [10–12, 15]. Using HRCT scans at 1-mm collimation, a lower attenuation threshold of -950 HU was found to correlate best with morphological emphysema [32]. However, the optimal threshold for the detection of emphysema on low-dose spiral CT has not been reported previously.

The authors acknowledge that the range of emphysema scores observed in the present study was smaller than would be expected. For the range of emphysema observed no compelling evidence was found to suggest that an increased percentage of emphysema was associated with an increased risk of lung cancer.

Although the results of this study suggest that percentage of emphysema based on quantitative CT measurements of lung density is not a significant risk factor for lung cancer after adjustment for sex, age and smoking history, several studies have suggested an increased risk of lung cancer associated with

emphysema. Recently, a 2–5% rate of unsuspected lung cancer was found on CT scanning in patients with severe emphysema who were undergoing evaluation for possible lung-volume reduction surgery [8, 9]. However, most of patients being evaluated for lung-volume reduction surgery have severe airway obstruction with an FEV1 of ⩽40 pred. On the basis of results from other studies [6, 7], the higher risk of lung cancer in patients undergoing lung-volume reduction surgery is more likely to be attributable to the presence of severe airway obstruction rather than anatomical emphysema.

Epidemiological studies have also reported increased risks of lung cancer in relation to the previous diagnosis of lung diseases, such as emphysema, chronic bronchitis and bronchial asthma [33, 34]. MAYNE *et al.* [33] conducted a population-based case-controlled study of lung cancer in male and female nonsmokers in New York. Statistically significant associations were found for previous history of emphysema (OR=1.94, 95% CI 1.10–3.43), chronic bronchitis (OR=1.73, 95% CI 1.10–2.72) and bronchial asthma (OR=1.82, 95% CI 1.26–2.63). BROWNSON *et al.* [34] also found a history of emphysema to be associated with an increased risk of lung cancer among females in Missouri (OR=2.7, 95% CI 1.8–4.2). However, the history of physician-diagnosed previous lung disease in these studies was based on self-report and therefore recall bias is a major concern [33, 34]. Another concern is that there may be misclassification among reported emphysema, chronic bronchitis and bronchial asthma.

Several mechanisms have been suggested to explain the predisposition of patients with COPD to developing lung cancer. Mucociliary clearance is impaired with COPD [35, 36]. During the clearing process, particles tend to pool in areas with impaired mucociliary clearance. This pooling may allow carcinogens from the smoke in the mucous blanket to have longer exposure time at these sites, leading to development of lung cancer [6]. COHEN *et al.* [37] have described familial clustering of pulmonary dysfunction in relatives of patients with lung cancer as well as in patients with COPD, suggesting that lung cancer and COPD share a common familial predisposition. There is increasing interest in whether carriers of an α_1-antitrypsin deficiency are at increased risk of lung cancer [34]. α_1-Antitrypsin deficiency accounts for <1% of COPD in the USA [3]. Although there are no reports of an increased risk of lung cancer in patients with homozygous α_1-antitrypsin deficiency, YANG *et al.* [38] recently demonstrated that lung cancer patients are significantly more likely to carry the mutated α_1-antitrypsin allele than the general population.

To conclude, the results of this study support the previous observation of an increased risk of lung cancer associated with airway obstruction, particularly severe obstruction. In addition, no compelling evidence was found to suggest that an increased percentage of emphysema, as assessed by quantitative computed tomography analysis using low-dose spiral computed tomography, is associated with lung cancer risk.

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