Association of Radiographic Emphysema and Airflow Obstruction with Lung Cancer

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Rationale: **To study the relationship between emphysema and/or airflow obstruction and lung cancer in a high-risk population.**

Objective: **We studied lung cancer related to radiographic emphysema and spirometric airflow obstruction in tobacco-exposed persons who were screened for lung cancer using chest computed tomography (CT).**

Methods: **Subjects completed questionnaires, spirometry, and low-dose helical chest CT. CT scans were scored for emphysema based on National Emphysema Treatment Trial criteria. Multiple logistic regressions estimated the independent associations between various factors, including radiographic emphysema and airflow obstruction, and subsequent lung cancer diagnosis.**

Measurements and Main Results: **Among 3,638 subjects, 57.5, 18.8, 14.6, and 9.1% had no, trace, mild, and moderate–severe emphysema, and 57.3, 13.6, 22.8, and 6.4% had no, mild (Global Initiative for Chronic Obstructive Lung Disease [GOLD] I), moderate (GOLD II), and severe (GOLD III–IV) airflow obstruction. Of 3,638 subjects, 99 (2.7%) received a lung cancer diagnosis. Adjusting for sex, age, years of cigarette smoking, and number of cigarettes smoked daily, logistic regression showed the expected lung cancer association with the presence of airflow obstruction (GOLD I–IV, odds ratio [OR], 2.09; 95% confidence interval [CI], 1.33–3.27). A second logistic regression showed lung cancer related to emphysema (OR, 3.56; 95% CI, 2.21–5.73). After additional adjustments for GOLD class, emphysema remained a strong and statistically significant factor related to lung cancer (OR, 3.14; 95% CI, 1.91–5.15).**

Conclusions: **Emphysema on CT scan and airflow obstruction on spirometry are related to lung cancer in a high-risk population. Emphysema is independently related to lung cancer. Both radiographic emphysema and airflow obstruction should be considered when assessing lung cancer risk.**

Keywords: emphysema; chronic obstructive pulmonary disease; lung cancer

The last 10 years have seen a rapid increase in the use of computed tomography (CT) (1, 2). Technological improvements have elevated CT to the diagnostic imaging modality of choice for many clinical indications, including pulmonary thromboembolism (3). Since the publication of the first Early Lung Cancer Action study in 1999 (4), CT screening for detecting early lung cancer in asymptomatic, high-risk persons has generated interest and controversy. High-risk persons are mostly current or ex-cigarette smokers, persons also at risk for emphysema and chronic airflow obstruction.

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Several studies imply a relationship between chronic obstructive pulmonary disease (airflow obstruction) and lung cancer, but very limited information about emphysema and lung cancer risk exists in the literature.

What This Study Adds to the Field

Emphysema is independently related to lung cancer. Both radiographic emphysema and airflow obstruction should be considered when assessing lung cancer risk.

The relationship between airflow obstruction and lung cancer was described over 20 years ago by Skillrud and colleagues (5) and Tockman and associates (6). A metaanalysis by Wasswa-Kintu and coworkers (7) showed that even a modest reduction in airflow significantly predicted lung cancer. Petty (8), in a thoughtful and prescient editorial, suggested that chronic obstructive pulmonary disease (COPD) and lung cancer could have common origins based on the same inflammatory disease process, with common genetic predisposition and environmental risk factors. Brody and Spira (9) further suggested that interindividual differences in genes that control genomic integrity and genes that control tissue injury may distinguish between lung cancer and COPD outcomes in response to inflammation caused by smoking. Intuitively, these hypotheses pertain to airflow obstruction and emphysema, two overlapping manifestations of chronic lung disease related to cigarette smoking.

In 3,638 current and ex-smokers screened with CT and evaluated with spirometry, we correlated visually graded emphysema severity on CT with emphysema risk factors and airflow obstruction. We then examined lung cancer related to airflow obstruction and radiographic emphysema. Our results showed that lung cancer is related to radiographic emphysema, independent of airflow obstruction.

METHODS

Participants

The Pittsburgh Lung Screening Study, a subproject of the University of Pittsburgh Lung Cancer Specialized Program of Research Excellence (SPORE), is a community-based study of lung cancer screening with low-dose multidetector helical CT. Beginning in early 2002, the investigators recruited and screened 3,642 volunteers, primarily from southwestern Pennsylvania, who met the following eligibility requirements: (*1*) 50–79 years of age; (*2*) current or ex-smoker of at least one-half pack of cigarettes per day for at least 25 years and, if no longer smoking, had quit smoking for no more than 10 years; (*3*) no personal history of lung cancer; (*4*) no chest CT scans within 12 months of enrollment; (*5*) body weight of

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400 pounds or less; and (*6*) provided informed, written consent. The University of Pittsburgh Institutional Review Board approved the study.

In addition to a low-dose multidetector helical CT, enrolled participants completed a written questionnaire and underwent spirometry for pulmonary function testing (PFT). The questionnaire obtained information about medical history, current health problems, signs and symptoms of pulmonary disease, occupation, and smoking history. The questionnaire asked participants if they had ever been told by a doctor that they had the following conditions: (*1*) chronic bronchitis, (*2*) emphysema, or (*3*) asthma. They were also asked if they ever had the following: (*1*) cough that produces blood, (*2*) cough that produces phlegm, (*3*) dry cough, (*4*) wheezing, or (*5*) shortness of breath.

Approximately 1 year (median, 1.05 yr; interquartile range, 1.02–1.11 yr) after initial screening, 95.3% of subjects who were still alive without a lung cancer diagnosis, had repeat CT screening. New funding permitted a third CT screening, which was received by 927 of the of 3,638 subjects (25.5%), a median of 3.26 years (interquartile range, 2.74–3.76 yr) after the baseline screening. The investigators contacted subjects annually to ascertain new diagnoses of lung cancer and obtained medical records, including pathology reports, to verify lung cancer endpoints. With the follow-up totaling over 13,000 person-years and averaging 3.7 years per subject, only 0.5, 2.3, and 15.9% were followed for reasons other than death or lung cancer diagnosis for fewer than 1, 2, and 3 years, respectively. Persons followed for less than than 2 years (2.3%) were lost to follow-up. The investigators retrieved medical records, including all pathology or cytology reports, to verify lung cancer diagnoses.

Spirometry Protocol

A trained technician, using an office-based OMI-3000 spirometer (OMI Spirometry System, Houston, TX), performed PFT without a bronchodilator in accordance with American Thoracic Society (ATS) criteria (10). The FEV_1 and FVC were measured, and the FEV_1/FVC ratio calculated. Hankinson's equations were used to calculate FEV_1 predicted from sex, race, age, and height (11). Throughout the study, an oversight committee maintained quality assurance by scrutinizing selected abnormal flow–volume loops. Feedback to the technicians resulted in greater than 90% of the flow–volume loops meeting ATS criteria for reproducibility. We used Global Initiative for Chronic Obstructive Lung Disease (GOLD) severity criteria based on post-bronchodilator FEV_1 to classify individuals into no, mild (GOLD I), moderate (GOLD II), and severe (GOLD III–IV) airflow obstruction categories (12).

CT Imaging Protocol

All chest CT scans were obtained on General Electric multidetector helical CT scanners during a single-breath hold at full inspiration. The scanning parameters were: tube current 40 mA, scanning time of one second per gantry rotation, and 140 kVp. Axial images were reconstructed with a high spatial frequency (lung) algorithm at contiguous 2.5 mm nonoverlapping intervals. CT images were viewed on a PACS monitor display system (STENTOR) (Richardson Electronics, Lafox, IL) using standard lung window settings (1,496/−555 Hounsfield units).

Protocol for Primary Interpretation of the Baseline Screening CT

Three readers, a pulmonologist (A.B.), a general radiologist (S.N.F.), and a chest radiologist (C.R.F.), visually scored the baseline CT scan for emphysema presence and severity. Scoring procedures used a five-level semiquantitative scale, based on National Emphysema Treatment Trial criteria, to represent no, trace, mild, moderate, and severe emphysema, the latter four categories roughly corresponding to emphysema affecting less than 10, 10–25, 25–50%, and greater than 50% of the lung, respectively (13). In a validation study involving 266 study subjects, a simple quadratic function of this five-level visual emphysema severity score explained 26% of the variance observed with a quantitative measure derived from CT densitometry. Details, including measures of inter-reader reliability, appear in the online supplement.

Data Analysis

We used chi-square tests to check for independence between baseline factors and emphysema severity and logistic regression (PROC Logistic, SAS version 9.1; SAS Institute, Cary, NC) to evaluate factors associated with lung cancer diagnosis. The analytic endpoint (biopsy-verified lung cancer diagnosis) included instances of lung cancer detected by the first CT screening and instances of lung cancer that became apparent only during follow-up. We used Wald tests and 95% confidence intervals (CIs) to evaluate statistical significance of individual risk factors, Hosmer-Lemeshow tests to check goodness of fit, and concordance statistics to measure prediction. After including sex and age, we identified the set of other demographic, smoking, and clinical risk factors that maximized lung cancer prediction (Table 1). A parsimonious multivariable logistic regression model with sex, age (in years), years of cigarette smoking, and cigarettes per day (in four categories) predicted lung cancer with a concordance statistic of 0.69. Subsequent models included airway obstruction or emphysema severity to measure associations independent of sex, age, and smoking. A model including both airway obstruction and emphysema evaluated mutual independence. Separate analyses modeled airway obstruction as a four-category variable (no, mild, moderate, and severe obstruction, represented by none, GOLD I, II, and III–IV, respectively), as a two-category variable (any and no obstruction), or as a continuous (single degree of freedom) ordinal variable (with no, mild, moderate, and severe obstruction represented by variable values of 0, 1, 2, and 3, respectively). Results were similar when we replaced GOLD class by two variables that represented the presence or absence of any obstruction (FEV_1/FVC <0.70 vs. FEV_1/FVC ≥ 0.70) and FEV_1 as a percentage of predicted. Separate analyses modeled emphysema as a four-category variable (representing no, trace, mild, and moderate–severe emphysema) or as a two-category variable (any and no emphysema). Using the appropriate cross-product term in logistic regression did not indentify any significant interactions ($P > 0.3$) between emphysema severity (four categories) and any other lung cancer risk factor (sex, age in years, years of smoking, cigarettes per day [four categories], and airway obstruction [four categories]). Statistical tests used a two-sided significance level of 0.05. Analytic approaches that accounted for differences in follow-up times produced the same results as logistic regression.

RESULTS

Subject Characteristics

After the removal of four Pittsburgh Lung Screening Study participants with incomplete PFT results, the final study group included 3,638 persons (48.6% women; 7.1% minority race or ethnicity; 57.4, 33.0, and 9.6% of persons aged 50–59, 60–69, and ≥70 yr). Three-fifths (60.2%) were current smokers and nearly half (48.2%) had smoked for 40 or more years. When asked about the average number of cigarettes smoked daily, 31.7, 42.5, 16.3, and 9.5% reported smoking less than 20, 20–29, 30–39, and 40 or more cigarettes per day, respectively. The distribution according to cigarette dose exposure (pack-years) was 18.3% (<30), 26.3% (30–44), 27.2% (45–59), 15.1% (60–74), and 13.2% (≥75). One-quarter (24.9%) reported a history of emphysema, bronchitis, or asthma, and two-thirds (67.5%) reported symptoms of cough, phlegm, or wheezing. Finally, 13.6, 22.8, and 6.4 had mild (GOLD I), moderate (GOLD II), and severe (GOLD III–IV) airflow obstruction and 18.8, 14.6, and 9.1% had trace, mild, and moderate–severe emphysema, respectively (Table 1).

Radiographic Emphysema Risk Factors

Factors associated with emphysema included sex ($P = 0.0025$), age ($P < 0.0001$), smoking status ($P = 0.0027$), years of cigarette smoking ($P < 0.0001$), number of cigarettes smoked per day ($P < 0.0001$), pack-years of smoking ($P < 0.0001$), history of emphysema, bronchitis, or asthma ($P < 0.0001$), and symptoms of cough, phlegm, or wheeze ($P < 0.0001$) (Table 1). Emphysema severity did not differ according to race and ethnicity ($P = 0.1207$). However, the small number of black subjects and subjects of other races may have limited our ability to detect differences.

The prevalence of moderate or severe emphysema was 3.3-fold greater in persons who were 70 years of age or older than in

TABLE 1. RADIOGRAPHIC EMPHYSEMA SEVERITY (PERCENTAGE DISTRIBUTION) ACCORDING TO SUBJECT CHARACTERISTICS

			Radiographic Emphysema Severity (*Row %*)†				
Characteristic	n	Total (%)	None (*n = 2,092*)	Trace (*n = 685*)	Mild (n = 530)	Mod–Severe (*n = 331*)	*P* Value*
Sex							0.0025
Men	1,871	51.4	54.6	20.3	15.8	9.2	
Women	1,767	48.6	60.6	17.3	13.2	8.9	
Age, yr							<0.0001
50–59	2,088	57.4	64.0	18.8	11.4	5.8	
60–69	1,199	33.0	51.7	18.8	17.8	11.8	
70+	351	9.6	38.5	19.4	22.8	19.4	
Race and ethnicity							0.1207
White, not Hispanic	3,381	92.9	57.1	18.7	15.1	9.1	
Black	200	5.5	62.5	21.5	8.0	8.0	
Other	57	1.6	61.4	19.3	8.8	10.5	
Smoking status							0.0027
Current smoker	2,190	60.2	55.3	20.0	15.8	8.9	
Ex-smoker	1,448	39.8	60.8	17.1	12.7	9.4	
Duration of cigarette use, yr							<0.0001
<40	1,885	51.8	65.1	18.4	10.6	5.9	
40+	1,753	48.2	49.3	19.3	18.8	12.5	
Dose intensity, cigarettes/d							<0.0001
<20	1,152	31.7	66.2	17.8	11.2	4.8	
20–29	1,547	42.5	55.7	19.1	15.2	10.0	
30–39	594	16.3	50.2	18.7	17.2	14.0	
40+	345	9.5	49.3	21.2	18.6	11.0	
Smoking intensity duration, pack-years							<0.0001
<30	666	18.3	73.1	17.4	7.1	2.4	
30–44	955	26.3	64.1	17.5	11.9	6.5	
45–59	989	27.2	53.5	18.4	18.2	9.9	
60–74	548	15.1	47.4	22.4	15.9	14.2	
75+	480	13.2	42.5	20.2	21.3	16.0	
History of emphysema, bronchitis, or asthma							<0.0001
No	2,731	75.1	60.6	19.3	13.8	6.2	
Yes	907	24.9	48.1	17.3	16.9	17.8	
Cough, phlegm, or wheeze							<0.0001
No	1,182	32.5	64.1	17.3	13.0	5.5	
Yes	2,456	67.5	54.3	19.5	15.3	10.8	
Airflow obstruction							<0.0001
None	2,085	57.3	72.4	18.4	7.4	1.8	
GOLD I	493	13.6	39.6	22.1	25.4	13.0	
GOLD II	828	22.8	39.1	20.4	23.3	17.1	
GOLD III–IV	232	6.4	27.2	10.3	24.6	37.9	

Definition of abbreviations: GOLD = Global Initiative for Chronic Obstructive Lung Disease; Mod = moderate.

* Independence between characteristic and radiographic emphysema severity, level of statistical significance (chi-square test).

† Row % is the percentage of the study subgroup total (n) with the indicated characteristic.

those who were 50–59 years of age; 2.1-fold greater in persons who had smoked for 40 years or more than persons who had smoked for fewer than 40 years; 2.3-fold greater in persons who smoked 40 cigarettes per day or more than in persons who smoked <20 cigarettes per day; and 6.7-fold greater in persons with 75 pack-years or more of cigarette smoke exposure than in those with fewer than 40 pack-years of cigarette smoke exposure. A history of emphysema, bronchitis, or asthma and symptoms of cough, phlegm, or wheeze were associated with a 2.9- and 2.0-fold greater prevalence of moderate or severe emphysema, respectively.

Airflow obstruction and emphysema correlated strongly; moderate or severe emphysema was 7.2-, 9.5-, and 21.1-fold more common in persons with mild, moderate, and severe airflow obstruction, respectively, than in persons without airflow obstruction. Although airway obstruction (as measured by diminishing FEV_1% predicted) increased with emphysema severity, emphysema severity–specific distributions of FEV_1% predicted showed substantial overlap (data not shown). The differences in mean FEV_1% predicted (95% CI) were −3.0 (−4.5, −1.5) for trace versus no emphysema, −9.2 (−10.8, −7.5) for mild versus no emphysema, and −20.3 (−22.4, −18.2) for moderate–severe versus no emphysema.

Factors Associated with Lung Cancer

Ninety-nine lung cancers (86 non–small cell and 13 small cell lung cancers) were diagnosed between 1 and 62 months of initial screening. As expected, lung cancer was associated with age ($P < 0.0001$), years of cigarette use ($P < 0.0001$), pack-years of cigarette smoke exposure ($P = 0.006$), and symptoms of cough, phlegm, or wheeze ($P = 0.048$). Lung cancer differences according to sex ($P = 0.99$), race and ethnicity ($P = 0.88$), smoking status ($P = 0.36$), cigarettes per day ($P = 0.09$), or self-reported history

TABLE 2. UNADJUSTED LUNG CANCER ASSOCIATIONS WITH DEMOGRAPHICS, SMOKING, AND MEDICAL HISTORY

	Lung Cancer			
Characteristic	Yes	No	OR	95% CI
Sex			(0.99)	
Men	51	1,820	Ref	
Women	48	1,719	1.00	0.67–1.49
Age, yr			(<0.0001)	
50–59	31	2,057	Ref	
60–69	48	1,151	2.77	1.75–4.37
70+	20	331	4.01	2.26–7.12
Race and ethnicity			(0.88)	
White, not Hispanic	93	3,288	Ref	
Black	5	195	0.91	0.36–2.26
Other	1	56	0.63	0.09–4.61
Smoking status			(0.36)	
Current smoker	64	2,126	Ref	
Ex-smoker	35	1,413	0.82	0.54–1.25
Duration cigarette use, yr			(<0.0001)	
<40	27	1,858	Ref	
40+	72	1,681	2.95	1.89–4.61
Dose intensity, cigarettes/d			(0.09)	
<20	27	1,125	Ref	
20–29	44	1,503	1.22	0.75–1.98
30–3 9	12	582	0.86	0.43–1.71
40+	16	329	2.03	1.08–3.81
Smoking intensity duration, pack-years			(0.006)	
<30	8	658	Ref	
30–44	21	934	1.85	0.81–4.20
45–59	27	962	2.31	1.04–5.11
60–74	21	527	3.28	1.44–7.46
75+	22	458	3.95	1.74–8.95
History of emphysema, bronchitis, or asthma			(0.09)	
No	67	2,664	Ref	
Yes	32	875	1.45	0.95–2.23
Cough, phlegm, or wheeze			(0.048)	
No	23	1,159	Ref	
Yes	76	2,380	1.61	1.00–2.58

Definition of abbreviations: CI = confidence interval; OR = odds ratio.

Values in parentheses indicate the statistical significance of association between the characteristic and lung cancer (Wald test *P* value).

of emphysema, bronchitis, or asthma ($P = 0.09$) were not statistically significant (Tables 2 and 3).

Totals of 41, 43, and 15 lung cancer cases were diagnosed after the first, second, and third CT screening, respectively. As single factors, both airflow obstruction ($P < 0.0001$) and emphysema ($P < 0.0001$) were strong determinants of lung cancer (Table 3). In an analysis adjusting for sex, age, years of cigarette smoking, and number of cigarettes smoked daily, lung cancer was diagnosed most frequently among persons with both emphysema and moderate – severe airflow obstruction (GOLD II–IV) (adjusted odds ratio [OR], 5.16; 95% CI, 2.79–9.57; Figure 1).

Adjusting for sex, age, years of cigarette smoking, and number of cigarettes smoked daily, logistic regression showed the expected lung cancer association with the presence of airflow obstruction (GOLD I–IV: OR, 2.09; 95% CI, 1.33–3.27; Table 3). A second logistic regression, also adjusting for sex, age, years of cigarette smoking, and number of cigarettes daily, showed lung cancer related to emphysema (OR, 3.56; 95% CI, 2.21–5.73; Table 3). Most notably, emphysema remained a strong and statistically significant factor (OR, 3.14; 95% CI, 1.91–5.15) after additional adjustments for GOLD class. After additional adjustments for emphysema severity, lung cancer associated with airflow obstruction lost statistical significance, except in an analysis that modeled GOLD class as an ordinal variable (*P* for trend = 0.0391).

Controlled for sex, age, years of smoking, cigarettes per day, and airflow obstruction, trace emphysema (OR, 2.48; 95% CI, 1.37–4.49), mild emphysema (OR, 4.43; 95% CI, 2.53–7.79), and moderate–severe emphysema (OR, 2.56; 95% CI, 1.26–5.20) were associated with lung cancer (Table 3 and Figure 2). An independent association between emphysema severity and lung cancer persisted in analyses that excluded subjects with one CT screening, in analyses that excluded subjects with more than two CT screenings, and in analyses limited to non–small cell lung cancer (data not shown).

DISCUSSION

This study examined the relationship among emphysema assessed semiquantitatively on CT scan, airflow obstruction based on spirometry, and lung cancer in the setting of a lung cancer screening study. The relationship between airflow obstruction and lung cancer has been well characterized (5–7, 14, 15). The Lung Health Study showed that the most common cause of death among subjects with airflow obstruction is lung cancer (16, 17). For any level of tobacco exposure, patients with chronic airflow obstruction have a greater risk for lung cancer than smokers without airflow obstruction (5), and this relationship is severity dependent. That is, individuals with the worst lung function have the highest risk (16, 17). In addition, independent of cigarette smoking history, reduced FEV_1 increases the risk for lung cancer in the general nonsmoking population (18).

We observed an increased frequency of lung cancer in subjects with emphysema, with the highest frequency observed in subjects with both emphysema and moderate–severe airflow obstruction (Figure 1). However, a test of interaction between airflow obstruction and radiographic emphysema had only borderline statistical significance ($P = 0.09$). Therefore, we speculated that airflow obstruction might enhance the lung cancer effect of emphysema. Using low-dose helical CT scanning to screen for lung cancer and emphysema at the same time can be efficient because the screened population is at risk for both diseases. The scoring system was relatively easy to use. The semiquantitative method did not appreciably add to the time required to interpret the scans for the detection of lung cancer and other significant chest abnormalities. With respect to lung cancer, our observation of an association with the mere presence of emphysema, at any level of severity, including trace (Table 3 and Figure 2), would appear to diminish the relevance of the method we used to quantify emphysema.

Validity was assessed by comparing emphysema scores with risk factors and PFT results. Overall, 42.5% of our population had CT evidence for emphysema with trace, mild, and moderate–severe emphysema present in 18.8, 14.6, and 9.1%, respectively. CT emphysema scores were analyzed according to sex, age, race and ethnicity, smoking status, smoking duration and intensity, and medical history. There were no statistically significant differences according to race or ethnicity ($P > 0.05$), but differences according to sex were significant ($P = 0.0025$). There were statistically significant increases in emphysema scores with advancing age, intensity and duration of smoking, symptoms, and airflow obstruction. Although not necessarily causal, the strong correlation between known emphysema risk factors and severity is noteworthy with respect to a validation of our emphysema scoring methodology. Although it is possible to have emphysema without airflow obstruction or airflow obstruction without em-

TABLE 3. MULTIPLE LOGISTIC REGRESSION ANALYSIS: UNADJUSTED AND ADJUSTED LUNG CANCER ASSOCIATIONS WITH AIRFLOW OBSTRUCTION AND RADIOGRAPHIC EMPHYSEMA

			Unadjusted		Adjusted*		Adjusted†	
	Cases	Noncases	OR	95% CI	OR	95% CI	OR	95% CI
Airflow obstruction			(<0.0001)		(0.0052)		(0.28)‡	
None	32	2,053	Ref		Ref		Ref	
GOLD I	16	477	2.15	1.17–3.95	1.66	0.89–3.11	1.13	0.59–2.17
GOLD II	36	792	2.92	1.80–4.73	2.11	1.27–3.49	1.47	0.87–2.50
GOLD III–IV	15	217	4.43	2.36–8.32	2.86	1.48–5.53	1.87	0.92–3.80
Airflow obstruction			(<0.0001)		(0.0014)		(0.16)	
None	32	2,053	Ref		Ref		Ref	
GOLD I–IV	67	1,486	2.89	1.89–4.43	2.09	1.33–3.27	1.41	0.87–2.29
Radiographic emphysema			(<0.0001)		(<0.0001)		(<0.0001)	
None	24	2,068	Ref		Ref		Ref	
Trace	22	663	2.86	1.59–5.13	2.58	1.43–4.66	2.48	1.37–4.49
Mild	37	493	6.47	3.83–10.9	5.04	2.94–8.62	4.43	2.53–7.79
Moderate–severe	16	315	4.38	2.30–8.33	3.20	1.65–6.23	2.56	1.26–5.20
Radiographic emphysema			(<0.0001)		(<0.0001)		(<0.0001)	
None	24	2,068	Ref		Ref		Ref	
Any	75	1,471	4.39	2.76–6.99	3.56	2.21–5.73	3.14	1.91–5.15

Definition of abbreviations: CI = confidence interval; GOLD = Global Initiative for Chronic Obstructive Lung Disease; OR = odds ratio.

Values in parentheses indicate the statistical significance of the indicated factor in multiple logistic regression models (Wald test *P* value).

* Adjusted for sex, age, years of cigarette smoking, and smoking dose intensity (four categories).

† Adjusted for sex, age, years of cigarette smoking, smoking dose intensity (four categories), and radiographic emphysema (four categories) or airflow obstruction (four categories), as appropriate.

‡ *P* for trend = 0.0391.

physema, airflow obstruction and emphysema correlate partially because emphysema is one of several COPD phenotypes and causes of airflow obstruction.

Emphysema as an independent risk factor for lung cancer has not been well studied. One study of the Mayo Clinic lung cancer screening population (19), using a quantitative analysis that measured emphysema score, found no increased frequency of lung cancer in 24 cases and 96 control subjects. Airflow obstruction, however, was a factor independently associated with lung cancer. There are inferences from the lung volume reduction literature that suggest that emphysema could be associated with lung cancer, as a 2–5% rate of unsuspected lung cancer has been found in this population of patients undergoing evaluation for possible lung volume reduction surgery (20, 21). Another study of a lung cancer screening population from Japan assessed the presence of emphysema (22). These investigators found less emphysema (2.9%) than our study, but the study population included 54.2% never-smokers. Another study suggested that emphysema is independently associated with lung cancer (23). In this smaller-scale study of a lung cancer screening population, de Torres and colleagues (23) found that the presence of emphysema on a CT scan, but not airflow obstruction, was associated with increased frequency of lung cancer. This study involved fewer subjects than ours (1,166 vs. 3,638) and included many fewer cancers (23 vs. 99). The populations were slightly different as well, with our subjects being older (mean age, 59 vs. 54 yr), better balanced in terms of sex (51 vs. 74% men), more intense smoking history (median, 47 vs. 33 pack-years), and more airflow obstruction (42.6 vs. 25%) and emphysema (42.5 vs. 29%). In addition, the de Torres study population was less well characterized with respect to smoking status, clinical status, and severity of airflow obstruction or emphysema, which limited the depth of their analyses. Nevertheless, the de Torres findings with respect to emphysema and lung cancer are similar to ours.

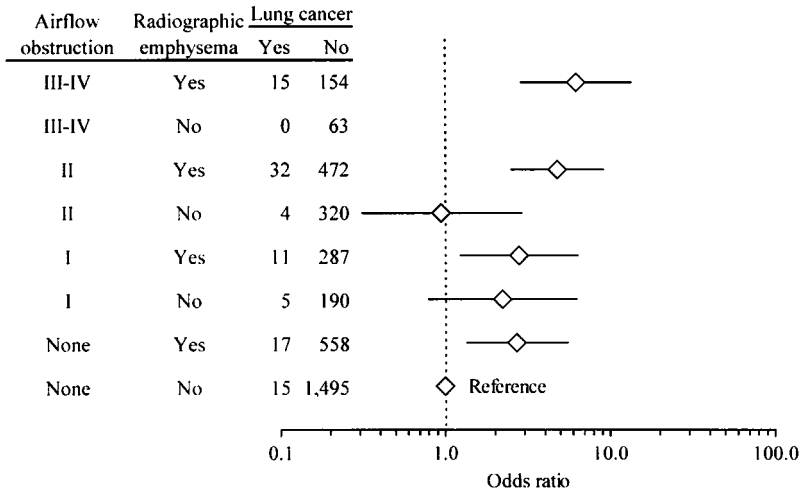

Figure 1. Lung cancer associations with airflow obstruction (Global Initiative for Chronic Obstructive Lung Disease [GOLD] stage) and radiographic emphysema, odds ratio (*diamonds*), and 95% confidence intervals (*whiskers*), adjusted for sex, age, years of cigarette smoking, and cigarette smoking dose intensity (in four categories).

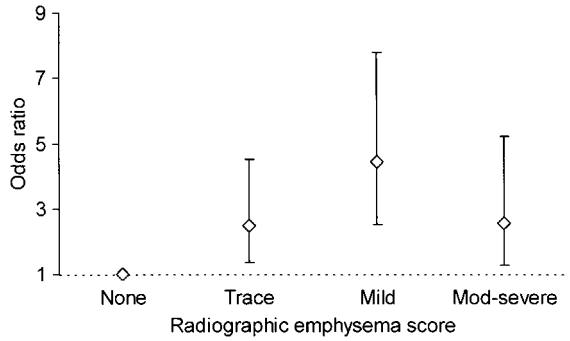

Figure 2. Association between radiographic emphysema and lung cancer (odds ratio and 95% confidence interval), adjusted for sex, age, years of cigarette smoking, cigarette smoking dose intensity (in four categories), and airflow obstruction (Global Initiative for Chronic Obstructive Lung Disease [GOLD] stage, in four categories).

In our study, both airflow obstruction and emphysema, independent of smoking, predicted lung cancer (Table 3). To compare airflow obstruction and emphysema as single measures in 50–79-year-old current and ex-cigarette smokers, we used our sex-, age-, and smoking-adjusted OR estimates and the observed four-level distributions according to airflow obstruction and emphysema to calculate population attributable risks (24). The results, population attributable risk values of 52% due to emphysema versus 32% due to airflow obstruction, point to the potential superiority of emphysema as a single measure of lung cancer risk.

The relationship between degree of emphysema and lung cancer is interesting. The severity of emphysema is related to smoking intensity (Table 1) and an examination of subjects with trace and mild emphysema suggests a dose–response effect where a greater burden of emphysema confers a greater risk of lung cancer (OR, 2.48–4.43). However, this trend is broken for subjects with moderate–severe emphysema (OR, 2.56). Potential explanations for this observation include (*1*) small sample size with associated statistical variability (Figure 2), (*2*) unrecognized selection factors causing a deficit in the number of study subjects with both lung cancer and moderate–severe emphysema, and (*3*) unknown factors that protected study subjects with moderate–severe emphysema from lung cancer.

There are several possible explanations for a relationship among lung function, emphysema, and lung cancer. The most intuitive and timely is a shared causal pathway from lung and airway inflammation. Tobacco smoke is well known to stimulate inflammation (25), and chronic inflammation has been suggested as an important factor in COPD (26) and emphysema (27). In fact, small airway obstruction has been described in both emphysema and COPD with the thickness of the walls of the small airways being closely associated with the severity of COPD (26) and emphysema (27). Chronic inflammation has also been implicated in the pathogenesis of many cancers (28), including lung cancer (29, 30). It certainly is plausible that chronic inflammation in the airways and lung, shown to be important in the pathogenesis of both emphysema and COPD, may result in repeated injury and repair, stimulating cell turnover and potential genetic errors, and ultimately lung cancer growth (31). A study in mice of bronchoalveolar stem cells provides further support for the concept of common pathogenesis (32). Bronchoalveolar stem cells exhibit proliferative capacity and self-renewal, responding in models of both lung injury and oncogenic K-ras stimulation. The fact that the presence of any emphysema, more so than the severity of emphysema, is associated with lung cancer in our study is consistent with a common pathogenesis for lung injury and repair and tumor proliferation.

The strength of this study is the use of CT screening and systematic follow-up to identify lung cancer cases. Every subject had an initial CT scan and 95.3% of those still at risk had a repeat CT test 1 year later. Follow-up at 2 years was 97.3% complete. The limitations of our study include the largely white population. Participants responded to mass mailings and may not be representative of the smoking population in general. Healthy responder bias may differentially lead to a less-diseased cohort. This may partially be offset by a self-selection bias in which participants who suspect something may be wrong tend to respond to screening invitations. Other limitations include the use of a subjective semiquantitative scoring system for emphysema determination. As a further validation of our study, the scores correlated with standard emphysema risk factors (age and cigarette-dose exposure) and spirometry-detected FEV_1%. In addition, the strong relationship between any emphysema and the development of lung cancer, in our analysis, tends to minimize the importance of the scoring system. Although our readers of emphysema were blinded to the clinical outcomes from screening, visible manifestations of lung cancer on CT may have influenced our readers' judgments regarding the presence or severity of emphysema. To evaluate this threat, we compared lung cancer cases and control subjects within each of three strata defined by lung cancer suspicion based on CT findings, including nodule characteristics. Unadjusted and adjusted for sex, age, and smoking, emphysema severity remained a statistically significant ($P < 0.05$) lung cancer predictor in each stratum (data not shown).

This study shows that both COPD, as manifested by GOLD stages I–IV, and emphysema are important factors related to lung cancer. The ability to refine the prediction of lung cancer risk in current and ex-smokers is likely to be increasingly important in the lung cancer screening debate. Incorporating factors such as family history, occupational exposures, presence of airflow obstruction, and emphysema with the standard lung cancer risk factors of age, smoking intensity and duration should allow a better risk assessment of high-risk populations in terms of lung cancer screening.

In conclusion, we have shown that both COPD as measured by GOLD I–IV and emphysema assessed semiquantitatively with the CT scan are independently related to lung cancer in a high-risk population, and that lung cancer occurs most frequently in patients with both COPD and emphysema.

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