Quantitative CT Assessment of Emphysema and Airways in Relation to Lung Cancer Risk¹

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Purpose:

To determine whether quantitative computed tomographic (CT) measurements of emphysema and airway dimensions are associated with lung cancer risk in a screening population.

Materials and Methods:

Institutional review board approval and informed consent for the use of deidentified images were obtained. In this retrospective study, CT scans were analyzed from 279 participants in the CT screening arm of the National Lung Screening Trial who were diagnosed with lung cancer and 279 participants who were not diagnosed with lung cancer after a median follow-up period of 6.6 years. Quantitative CT measurements of emphysema and right upper lobe apical segmental and subsegmental airway dimensions, and multiple patient history-related variables, were compared between the two groups. Significant variables were tested in multivariate models for association with lung cancer by using multiple logistic regression.

Results:

The emphysema index of percentage upper lung volume less than -950 HU had the strongest association with lung cancer (mean, 10.7% [standard deviation, 13.5] in patients vs 7.2% [standard deviation, 10.4] in control subjects; $P < .001$), but the relationship was weak ($R^2 = 0.015$, $P < .001$, $c = 0.57$). No CT measures of emphysema had an association with lung cancer independent of the patient medical history variables. Airway dimensions were not associated with lung cancer.

Conclusion:

Quantitative CT measurements of emphysema but not airway dimensions were only weakly associated with lung cancer, demonstrating no potential practical value for clinical risk stratification.

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Identification of factors associated with lung cancer in smokers may help to identify those at relatively lesser or greater risk. Moderately accurate risk prediction models for lung cancer have been developed on the basis of readily obtainable information, such as smoking history; age; and medical, occupational, and family history (1–3). Incorporation of risks identifiable through clinical testing into prediction models may further increase their predictive value. One such risk that has been identified is airflow obstruction caused by chronic obstructive pulmonary disease (COPD) (4–6). Chronic inflammation in response to cigarette smoke has been cited as a plausible common etiologic factor, as it may lead to both lung cancer and to the airway wall thickening and emphysema that often occur in COPD (7,8).

The degree of airflow obstruction in COPD is related to both emphysema and airway wall thickening on computed tomographic (CT) scans (9–11). It has been found that visually identified emphysema on CT scans in lung cancer screening populations is a risk factor for lung cancer, independent of airflow obstruction (12,13). To our knowledge, airway wall thickening has not been previously investigated for an association with lung cancer.

While visual identification of emphysema on CT scans may allow further stratification of lung cancer risk, the visual assessment of emphysema on CT images is a subjective task known to be prone to observer variability (14,15). This variability can be nearly eliminated by quantifying emphysema through computer-automated measurements of lung attenuation. Relatively newer, objective computerized image analysis techniques for the quantitative determination of airway dimensions also are now available. Thus, computerized image analysis of emphysema and airway dimensions may be useful for refining lung cancer risk estimates among smokers in whom CT has been performed in the screening or diagnostic setting. We conducted this study to determine whether quantitative CT measurements of emphysema and airway dimensions are associated with lung cancer risk in a screening population.

Materials and Methods

Subjects and Clinical Data

This retrospective study involving participants enrolled in the National Lung Screening Trial (NLST) (16) was approved by the institutional review board at Washington University School of Medicine (St Louis, Mo) and by the Data and Safety Monitoring Board of the NLST.

The subjects had previously consented to the use of their deidentified CT images in other research studies.

The NLST, in which lung cancer mortality rates after three annual screening examinations performed by using either chest radiography or chest CT were compared, enrolled over 53 000 individuals between the ages of 55 and 74 years with a minimum smoking history of 30 pack-years. Other enrollment criteria and trial design features have been previously described (16). A total of 285 participants in the CT screening arm of the Lung Screening Study (LSS) component of the NLST who received a diagnosis of lung cancer at any time between their first screening

Advances in Knowledge

- The emphysema index at a threshold level of -950 HU in the upper one-third of the lungs was the quantitative emphysema parameter most strongly related to lung cancer occurrence in a high-risk screening population ($P < .001$), but the relationship was weak ($R^2 = 0.015$).
- Quantitative measurements of right upper lobe apical segmental and subsegmental airway dimensions, including wall thickness, wall area, wall area percentage, and inner perimeter length, were not related to lung cancer occurrence ($P \geq .25$) in a high-risk screening population.

Implications for Patient Care

- Quantitative measurements of emphysema and airway dimensions would not be helpful for distinguishing which individuals in a screening population of older, heavy smokers are at reduced or increased risk of lung cancer.
- Similar to the known variation in extent of emphysema, airway wall thickening, and chronic obstructive pulmonary disease among smokers, the variable occurrence of lung cancer may reflect the underlying heterogeneity of the biological response to long-term cigarette smoking among different individuals.

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Abbreviations:

COPD = chronic obstructive pulmonary disease

EI = emphysema index

EI-910 = EI at a threshold level of -910 HU

EI-950 = EI at a threshold level of -950 HU

FWHM = full width at half maximum

LSS = Lung Screening Study

NLST = National Lung Screening Trial

OR = odds ratio

PC = phase congruency

RB1 = right upper lobe apical segment bronchus

RB1_a = first branch of RB1

RB1_{a1} = first branch of RB1_a

Author contributions:

Guarantor of integrity of entire study, D.S.G.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; literature research, D.S.G., P.G., M.T.D.; clinical studies, P.A.K.; experimental studies, D.S.G.; statistical analysis, D.S.G., P.G., B.J.N., T.K.P.; and manuscript editing, D.S.G., M.T.D., P.A.K., D.A.L.

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See also the editorial by Carrozzi and Viegi in this issue.

examination and June 2008 were randomly selected from all LSS group participants. An equal number of control subjects who did not receive a diagnosis of lung cancer (the control subjects) also were randomly selected. Because CT technical parameters may affect quantitative emphysema measurements (17–19), subject selection was designed to ensure the same frequency of different technical parameter combinations (CT scanner model, section thickness, section interval, reconstruction kernel, and reconstruction software version) for the CT scans of both groups.

After completion of all measurements at the time of final statistical analysis, it was ascertained that, in six control subjects, lung cancer had developed; these six original control subjects and their CT technical parameter-matched patients were excluded, so that 279 patients and 279 control subjects were eligible for analysis. For the control subjects, the median follow-up period after the first screening CT was 6.6 years (range, 0.9–7.2 years), and follow-up was at least 5.9 years in 90% (493 of 548).

Clinical data had been collected by means of participant completion of study forms and were available for all 558 subjects. Clinical data were classified as either demographic and social history variables (age, sex, race or ethnicity, body mass index, smoking history, alcohol use, highest education level, and work history) or medical history variables (previous medical diagnoses and family history of cancer). Data were obtained from the LSS Data Coordinating Center of the NLST (Westat, Rockville, Md).

The final study population comprised 39% women (215 of 558) and 61% men (343 of 558), with a mean age of 62 years (standard deviation, 5). The percentage of subjects in each of the racial and ethnic categories was 91% (506 of 558) for white, 4% (23 of 558) for black or African American, 3% (14 of 558) for Asian, and less than 1% each (15 of 558, 3% total) for all other categories (American Indian or Alaska Native, Native Hawaiian, or other Pacific Islander, and multiracial). The median smoking history was 52 pack-years (range, 30–221

pack-years), and 54% (304 of 558) were current smokers.

CT Scan Acquisition

The CT scans that were analyzed were from the baseline screening examinations performed between October 2002 and May 2004, and the examinations were performed with multidetector scanners with a minimum of four detector rows. All screening examinations had been performed without intravenous contrast material by using a low-radiation dose technique. Technical parameters of the scanning protocol were: 120–140 kVp, 40–80 mAs, pitch of 1.25–2.00, 20–60 effective mAs, 1.0–2.5-mm section thickness, 512×512 matrix, and contiguous or overlapping section interval. Scanner models and reconstruction parameters are provided in Table E1 (online). All CT scanners underwent performance testing to ensure compliance with American College of Radiology accreditation criteria, and water phantom data were monitored bimonthly by the LSS-NLST Quality Assurance Working Group. The CT images were obtained from the CT Image Library of the LSS component of the NLST (20).

Emphysema Analysis

Emphysema was quantified by using a pulmonary dedicated software package (Pulmonary Analysis Software Suite Emphysema Profiler; Vida Diagnostics, Iowa City, Iowa). The lungs were semiautomatically segmented, and an emphysema index (EI) was quantified as the percentage of all lung voxels having attenuation lower than -950 HU (EI at a threshold level of -950 HU [EI-950]). The EI at higher threshold levels does not correlate as strongly with quantitative histologic measurements of emphysema as the EI at lower threshold levels does (18,19) and, therefore, is less specific for emphysema. However, because a higher threshold level would likely capture some subjects with milder emphysema that might be missed by using the lower threshold level, the EI at a threshold level of -910 HU (EI-910) also was obtained. Because emphysema in smokers tends to predominate in the upper lobes, separate measurements of

the EI-950 in the upper, mid, and lower one-third of the lungs, determined according to lung height, were obtained. Seven patients with CT scans in whom the automated segmentation process failed, and their CT technical parameter-matched control subjects, were excluded. Thus, quantitative emphysema data were available for 544 patients and control subjects combined.

Airway Analysis

Airway dimensions were measured on transverse CT sections by using an open-source image analysis software program (Airway Inspector; <http://www.airway-inspector.org/>). The inner and outer airway walls were identified by using both the full width at half maximum (FWHM) and phase congruency (PC) edge-detection methods (21). The cross-sectional airway parameters included the average wall thickness, total wall area, inner perimeter length, and the percentage of the total cross-sectional area of the airway composed of airway wall (wall area percentage). These features were measured for the right upper lobe apical segment bronchus (RB1) at the approximate midpoint between the right upper lobe bronchus and the RB1 branch point. Two subsequent generations along the RB1 path (first branch of RB1 [RB1_a] and first branch of RB1_a [RB1_{ai}]) also were measured approximately midway between their proximal and distal branch points. These airways were chosen because they are round or nearly round in transverse cross section, and they are readily identifiable in most scans. In addition, the dimensions of RB1 airways have been shown to correlate with the degree of airflow obstruction in COPD (10,22), with the CT dimensions of other airways in smokers (10), and with the thickness of the small airways not resolved with CT but which represent the site at which airflow obstruction occurs (23). We also adjusted the wall thickness and inner perimeter length for subject height as a potential means of normalizing these measurements for variability in lung size across individuals. After excluding scans of those with lung cancer and their CT technical parameter-matched control subjects for

which airway segmentation failed, the numbers of subjects with measurements available for RB1, RB1_a, and RB1_{ai} were 444, 442, and 410, respectively (FWHM method), and 460, 458, and 404, respectively (PC method).

Data Analysis

Associations between variables and lung cancer status were evaluated by using the Student *t* test (for independent samples) (continuous variables) or contingency table tests (categorical variables) and odds ratios. Except for sex, only variables for which *P* < .1 were further tested by using multiple logistic regression with backward selection to retain variables significant at the *P* < .05 level. Multiple logistic regression models to predict lung cancer status were developed by using demographic and social history variables only; medical history variables only; demographic, social history, and medical history variables only; CT variables only; and all variables. The predictive value of the models was assessed by using the model *R*², which indicates the explanatory value of the model, and the concordance statistic *c*, which indicates the proportion of cases correctly diagnosed by the model (24,25). Emphysema was entered as either a continuous variable (EI) or as a binary categorical variable in separate models. The attenuation threshold level used for the binary groupings was determined by evaluating multiple threshold levels at increments of 5 index percentage points and by using the threshold level having the strongest association with lung cancer status (lowest *P* values in contingency table tests). Because the distributions of the whole-lung EI-950 and upper-lung EI-950 were skewed toward low values, they were tested in the models without and with log transformation. Statistical analyses were performed, and models were developed by using software (JMP 8.0; SAS Institute, Cary, NC).

Results

Univariate Comparisons

Among demographic and social history variables (Table 1), age and pack-years

Table 1

Demographic, Social, and Medical History Variables Compared between 279 Patients and 279 Control Subjects

Characteristic	Patients	Control Subjects	<i>P</i> Value	Unit OR*
Demographic and social history				
Age (y) [†]	63.4 (5.3)	61.0 (4.8)	<.0001	1.10 (1.06, 1.14)
Sex			.93	
No. male	171	172		Reference
No. female	108	107		1.02 (0.72, 1.43)
Body mass index (kg/m ²) [†]	26.7 (4.5)	28.3 (5.4)	.0002	0.94 (0.91, 0.97)
Smoking (pack-years) [†]	66.8 (28.4)	53.0 (21.2)	<.0001	1.02 (1.02, 1.03)
Smoking status			.13	
No. former smokers	118	136		Reference
No. current smokers	161	143		1.30 (0.93, 1.81)
Race or ethnicity			.7	
No. white	253	253		Reference
No. black or African American	13	10		1.3 (0.56, 3.09)
No. other	13	16		0.81 (0.38, 1.72)
Highest education level			.13	
No. high school graduates	64	68		Reference
No. less than high school graduate	29	19		1.62 (0.83, 3.21)
No. with some college or other training	111	113		1.04 (0.68, 1.61)
No. with bachelor's degree or higher	75	79		1.01-(0.63, 1.61)
Alcohol use [‡]			.18	
No. with none	70	52		Reference
No. with any	208	226		0.84 (0.61, 1.11)
Work history				
Asbestos [§]			.54	
No	263	267		Reference
Yes	15	12		1.27 (0.58, 2.82)
Chemicals or meat manufacturing			.47	
No	261	265		Reference
Yes	18	14		1.31 (0.64, 2.72)
Farming			.3	
No	249	241		Reference
Yes	30	38		0.76 (0.46, 1.27)
Foundry or steel mill			.7	
No	263	265		Reference
Yes	16	14		1.15 (0.55, 2.44)
Painting			.68	
No	268	266		Reference
Yes	11	13		0.84 (0.36, 1.91)
Welding			.12	
No	256	265		Reference
Yes	23	14		1.70 (0.87, 3.45)
Medical History				
Adult asthma			.009	
No	271	257		Reference
Yes	8	22		0.34 (0.14, 0.76)
Bronchiectasis			.07	
No	275	268		Reference
Yes	4	11		0.35 (0.10, 1.1)
Chronic bronchitis			.66	
No	255	252		Reference
Yes	24	27		0.88 (0.49, 1.56)

Table 1 (continued)

Table 1 (continued)

Demographic, Social, and Medical History Variables Compared between 279 Patients and 279 Control Subjects

Characteristic	Patients	Control Subjects	P Value	Unit OR*
Emphysema			.0002	
No	245	269		Reference
Yes	34	10		3.73 (7.87, 8.12)
COPD			.0002	
No	251	272		Reference
Yes	28	7		4.33 (1.96, 10.94)
Pneumonia			.61	
No	220	215		Reference
Yes	59	64		0.90 (0.60, 1.34)
Diabetes			.77	
No	253	251		Reference
Yes	26	28		0.92 (0.52, 1.62)
Hypertension			.72	
No	176	180		Reference
Yes	103	99		1.06 (0.75, 1.50)
Heart disease or heart attack			.71	
No	240	243		Reference
Yes	39	36		1.10 (0.67, 1.79)
Any cancer			.86	
No	260	261		Reference
Yes	19	18		1.06 (0.54, 2.08)
Family history of cancer			.16	
No	204	220		Reference
Yes	69	56		1.33 (0.89, 1.99)

Note.—Variables for which there were fewer than 20 positive responses all had *P* values greater than .1 and are not shown. These variables included the following: work history of baking, butchering or meat packing, coal mining, cotton or jute processing, firefighting, grain milling, hard rock mining, or sandblasting; medical history of asbestosis, lung fibrosis, childhood asthma, bronchiectasis, sarcoidosis, silicosis, tuberculosis, and stroke; and specific cancer diagnoses (bladder, breast, cervical, esophageal, colorectal, kidney, laryngeal, oral, nasal, pharyngeal, stomach, thyroid, and transitional cell). OR = odds ratio.

* Numbers in parentheses are 95% confidence intervals.

† Values are means, and numbers in parentheses are standard deviations, except where otherwise indicated.

‡ One patient and one control subject had no response.

§ One patient had no response.

|| Six patients and three control subjects had no response.

had a strong positive association and body mass index had a negative association with lung cancer status. Current smoking status, alcohol consumption, race or ethnicity, education, and work history were not associated with lung cancer at the $P < .1$ level. While lung cancer was not more frequent among the 26 individuals who reported a history of work exposure to asbestos, the exposure duration was less than 10 years in half of them and was more than 20 years in only seven (six of whom had lung cancer).

Among medical history variables (Table 1), adult asthma and bronchiectasis were associated with fewer cases

of lung cancer, while COPD and emphysema were associated with more cases of lung cancer. A history of COPD and a history of emphysema had similar associations with lung cancer and were combined as a single variable in the multivariate analyses. A history of chronic bronchitis, previous malignancy, and a family history of lung cancer were not associated with lung cancer.

The population was skewed toward the lower range of EI-950 values (Figure). Among continuous CT measures of emphysema, the whole-lung EI-950, whole-lung EI-910, upper- and mid-lung EI-950, and upper- and mid-lung EI-910 were associated with lung cancer

status (Figure, Table 2). These parameters were correlated to each other ($r = 0.76$ – 0.99 , $P < .0001$ for all comparisons). The upper-lung EI-950 had the strongest association with lung cancer (lowest *P* value) when the raw data were used (Figure), and it also had a very strong association when log-transformed data were used (Table 2). In the categorical assessment of emphysema, the binary classification defined by an upper-lung EI-950 threshold level of 25% had the strongest association with lung cancer status (Table 3).

None of the airway measures differed between patient and control subject groups (Table 4). The wall thickness and inner perimeter both decreased, and the wall area percentage increased, at more distal airway generations. The wall thickness was larger and the inner perimeter was smaller when measured by using the FWHM method rather than the PC method (data not shown), but FWHM and PC measurements were correlated at each airway generation ($r = 0.61$ – 0.94 , all $P < .001$).

Multiple Logistic Regression Models

In the model that was based on demographic and social history variables alone, age, pack-years, and body mass index were independently related to lung cancer status (model $R^2 = 0.105$, $P < .0001$, $c = 0.72$). Sex was nearly significant ($P = .07$), and including it in the model only marginally increased the model R^2 ($R^2 = 0.110$, $P < .0001$, $c = 0.72$). The model that was based on medical history variables alone included a history of adult asthma and a history of COPD or emphysema (model $R^2 = 0.0421$, $P < .0001$; $c = 0.58$). Table 5 shows the model in which the variables retained in the demographic and social history model and the medical history model were combined, and again including sex (model 1); all variables were retained, and sex became significant with $P = .02$ (model $R^2 = 0.142$, $P < .0001$, $c = 0.74$).

To determine whether characterization of emphysema by combining the EI-950 and EI-910 may be more strongly associated with lung cancer than the individual EI-950 and EI-910 measurements, logistic regression by using backward

selection was performed with all six continuous emphysema variables (whole-, upper-, and mid-lung EI-950 and EI-910). The upper-lung EI-950 was the only variable independently associated with lung cancer, and the relationship was weak (model $R^2 = 0.015$; $P < .001$; OR = 11.7 over entire 0%–60% range; 95% confidence interval: 2.72, 54.3; $c = 0.57$). When the log-transformed EI-950 values were used, the whole-lung EI-950 was the only variable associated with lung cancer, and the relationship was even weaker ($R^2 = 0.008$; $P = .01$; unit OR = 1.16; 95% confidence interval: 1.03, 1.31; $c = 0.56$).

When the continuous (upper-lung EI-950) and categorical (upper-lung EI-950 $\geq 25\%$) quantitative emphysema variables most strongly associated with lung cancer were tested as input variables in multiple logistic regression models along with the variables in the model in which demographic, social history, and medical history parameters were combined (Table 5, model 1), they were not retained in the model. Thus, these quantitative emphysema variables were not associated with lung cancer independent of the variables in model 1 (Table 5). This also held for the other quantitative emphysema parameters.

When the binary variable indicating whether the upper-lung EI-950 was 25% or more was substituted for a history of COPD or emphysema in model 1, it was retained, although the model R^2 and concordance statistic were slightly lower ($R^2 = 0.1284$, $P < .0001$, $c = 0.73$) (Table 5, model 2). Thus, the upper-lung EI-950 as a binary variable was weakly associated with lung cancer occurrence independent of the model 1 demographic, social history, and medical history parameters other than a history of COPD or emphysema. Neither the upper-lung EI-950 as a continuous variable ($P = .08$) nor the whole-lung log-transformed EI-950 ($P = .32$) or other quantitative emphysema parameters were retained when substituted in the model for a history of COPD or emphysema.

Discussion

In the univariate analyses, individuals with lung cancer had a greater extent of

Dot plot graphs illustrate the distribution of CT EI parameters with significant differences ($P < .05$) between patients (cases) and control subjects; P values are for two-tailed unpaired t tests. Solid lines = means.

emphysema as measured with multiple quantitatively determined CT parameters of lung attenuation. As in previous studies in which subjective assessment of emphysema was used (12,13), the ORs in our univariate analyses revealed a significantly higher likelihood of lung cancer in persons with a greater quantitative amount of emphysema. However, although the relationship was significant ($P < .001$ for the upper-lung EI-950), the size of the effect was almost negligible ($R^2 = 0.015$). Moreover, the c statistic of 0.57 for the upper-lung EI-950 indicates that the predictive model for this quantitative emphysema parameter assigned a higher likelihood of being in the cancer group to the patient rather than to the control subjects only 57% of the time, little higher than chance. Multivariate modeling revealed that quantitative emphysema assessment was not

associated with lung cancer independent of a history of COPD or emphysema and did not serve as a robust replacement for this parameter in the models. Thus, our findings suggest that the CT quantification of emphysema would have little to no value for identifying those individuals in a high-risk screening population who are at greatest or least risk of having lung cancer and would provide no additional benefit to clinical information in this regard.

To our knowledge, investigators in no other studies have reported a difference in quantitative emphysema measurements between subjects with and without lung cancer. Researchers in two smaller case-control studies, performed in a single-center screening population in which subjects were matched according to sex, age, and smoking history (26,27), found that quantitative

Table 2

Univariate Associations of Continuous Emphysema Measurements with Lung Cancer Status

Measurements	Patients	Control Subjects	P Value	OR*
Whole lung				
EI-950	9.1 (10.8)	6.8 (8.8)	.006	1.02 (1.01, 1.04)
lnEI-950	1.4 (1.4)	1.1 (1.4)	.012	1.16 (1.03, 1.31)
EI-910	27.6 (17.9)	23.8 (16.3)	.009	1.01 (1.00, 1.02)
Upper lung				
EI-950	10.7 (13.5)	7.2 (10.4)	.0009	1.02 (1.01, 1.04)
lnEI-950	1.4 (1.6)	1.0 (1.6)	.004	1.17 (1.05, 1.30)
EI-910	29.3 (19.7)	24.5 (17.5)	.0028	1.01 (1.00, 1.02)
Mid lung				
EI-950	8.6 (11.0)	6.3 (8.6)	.0075	1.02 (1.01, 1.04)
lnEI-950	1.3 (1.5)	1.0 (1.4)	.03	1.13 (1.01, 1.27)
EI-910	27.8 (18.8)	23.8 (16.6)	.009	3.56 (1.37, 9.38)
Lower lung				
EI-950	8.3 (9.9)	7.1 (8.8)	.15	1.01 (0.99, 1.03)
lnEI-950	1.3 (1.5)	1.1 (1.5)	.1	1.01 (0.98, 1.23)
EI-910	25.4 (17.4)	22.8 (16.5)	.08	2.45 (0.91, 6.68)

Note.—Data are mean percentages, except where otherwise indicated. Numbers in parentheses are standard deviations, except where otherwise indicated.

* Numbers in parentheses are 95% confidence intervals.

Table 3

Univariate Associations of Categorical Emphysema Measurements with Lung Cancer Status**A: Association between Whole-lung EI-950 and Lung Cancer***

Clinical Data	Whole-lung EI-950 < 15%	Whole-lung EI-950 ≥ 15%
No. of cancers	215	57
Total no. in category	455	89
Percentage	47	64

B: Association between Upper-lung EI-950 and Lung Cancer†

Clinical Data	Upper-lung EI-950 < 25%	Upper-lung EI-950 ≥ 25%
No. of cancers	230	42
Total no. in category	485	59
Percentage	47	71

* $P = .004$.

† $P = .00047$.

measurements of emphysema were not associated with lung cancer, independent of measures of airflow obstruction. This held whether emphysema was considered as a continuous variable or subjects were classified as having an EI at a threshold level of -900 HU either above or below 15%. Results of univariate analyses for associations between emphysema and lung cancer and between lung cancer and demographic or subject history variables were not reported.

Investigators in two previous studies (12,13) in which screening CT scans were assessed visually found that the presence of any emphysema was independently associated with lung cancer, after adjusting for sex, age, and smoking, with an OR for cancer of approximately 2.5–3.5. In our study, an OR of 1.95 was found when subjects were classified as having an upper-lung EI-950 above or below 25%, which is probably equivalent to at least a moderate amount

of emphysema. A quantitative threshold level for distinguishing between no emphysema and any emphysema has not been established, but the lower dividing points for binary classification tested in our study were less strongly associated with lung cancer status. It should be noted that the correlation between visual and quantitative assessments is imperfect (14), implying that they reveal somewhat different features. However, because subjective reviewers cannot be blinded to many obvious lung cancers, there is a greater potential for bias in visual assessment.

There was no relationship between RB1 airway dimensions and lung cancer. This was true even for the segmental branches, for which the relationship to airflow obstruction is stronger than the segmental branch (22). The FWHM method of airway edge detection has been used in multiple studies, but it is known to lead to overestimation of airway wall thickness (28). However, our results were the same with the PC method, which provides lower estimates of wall thickness and may be more accurate (21). The lack of a detectable relationship between lung cancer and airway dimensions over multiple bronchial generations with both methods strongly suggests that CT measurements of airways would not be helpful for estimating lung cancer risk. It also may indicate that airway remodeling and lung cancer in smokers arise from different cellular and molecular pathways. While a larger sample size may have increased the ability to detect a difference, we calculated that ours was more than large enough to detect a fairly small difference in airway parameters between patients and control subjects of 0.2 standard deviations at $\alpha = .05$.

In the multiple logistic regression model, quantitative emphysema was significantly associated with lung cancer only when a history of COPD or emphysema was not entered in the model, and this model had lower clinical predictive ability than the model that included a history of COPD or emphysema, as shown by its lower R^2 value. Thus, a history of COPD or emphysema

Table 4

PC Airway Measurements for Each Bronchial Generation

Measurement	RB1 (n = 460)		RB1 _a (n = 458)		RB1 _{all} (n = 404)	
	Patients	Control Subjects	Patients	Control Subjects	Patients	Control Subjects
WT (mm)	1.51 (0.14)	1.50 (0.14)	1.42 (0.12)	1.42 (0.12)	1.34 (0.11)	1.35 (0.11)
WT/height (mm/m)	0.87 (0.09)	0.87 (0.08)	0.82 (0.07)	0.82 (0.07)	0.78 (0.07)	0.77 (0.06)
WA (mm ²)	27.8 (7.0)	27.8 (6.3)	20.1 (4.8)	20.1 (4.5)	14.6 (3.8)	15.0 (3.5)
WA/height (mm ² /m)	16.0 (3.83)	15.9 (3.35)	11.6 (2.60)	11.6 (2.42)	0.21 (0.05)	0.22 (0.05)
WA%	65.9 (7.2)	65.3 (7.5)	73.6 (6.7)	73.3 (6.7)	80.6 (5.1)	80.1 (4.9)
Pi (mm)	13.4 (3.6)	13.6 (3.5)	9.5 (2.6)	9.5 (2.5)	6.5 (1.9)	6.7 (1.8)
Pi/height (mm/m)	7.72 (1.98)	7.81 (1.91)	5.46 (1.43)	5.48 (1.41)	3.75 (1.04)	3.85 (0.96)

Note.—Data are means. Numbers in parentheses are standard deviations. $P = .25-.9$ for differences between patients and control subjects at each bronchial generation. Pi = inner perimeter length, Pi/height = Pi normalized for height, WA = cross-sectional wall area, WA/height = WA normalized for subject height, WA% = WA/total cross sectional airway area multiplied by 100, WT = cross-sectional wall thickness, and WT/height = WT normalized for subject height.

Table 5

Multiple Logistic Regression Analysis of Variables Associated with Lung Cancer Status

Parameter	OR*	PValue
Model 1[†]		
Age (y)	1.09 (1.05, 1.13)	6.86E-6
Female sex	1.58 (1.06, 2.37)	.0244
Smoking (pack-years)	1.03 (1.02, 1.03)	5.28E-8
Body mass index (kg/m ²)	0.95 (0.91, 0.98)	.0059
History of adult asthma	0.16 (0.05, 0.43)	.0005
History of COPD or emphysema	3.41 (1.78, 6.94)	.0004
Model 2[‡]		
Age (y)	1.09 (1.05, 1.13)	.00001
Female sex	1.62 (1.09, 2.42)	.017
Smoking (pack-years)	1.03 (1.02, 1.04)	1.46E-8
Body mass index (kg/m ²)	0.95 (0.91, 0.98)	.0040
History of adult asthma	0.22 (0.08, 0.57)	.0030
Upper lung EI-950 $\geq$ 25%	1.95 (1.03, 3.79)	.0438

*Numbers in parentheses are 95% confidence intervals.

[†] $R^2 = 0.142$, $P < .0001$, $c = 0.74$

[‡] $R^2 = 0.128$, $P < .0001$, $c = 0.73$.

was more strongly associated with lung cancer than quantitative emphysema, and airway dimensions were not associated with lung cancer. One possible explanation for this is that a clinical diagnosis of COPD or emphysema depends on symptoms and lung function, as well as imaging findings, and symptoms and lung function are only moderately correlated to quantitative CT measurements of emphysema. Furthermore, a clinical diagnosis of COPD or emphysema may not be made until the disease is relatively advanced. Hence,

a clinical diagnosis may reflect even greater susceptibility to the effects of cigarette smoke than an elevated CT EI does and, consequently, may reflect a greater risk of lung cancer. While there is an element of unreliability to such self-reported medical history data, the association between a history of COPD or emphysema and lung cancer in our study is consistent with the findings of other studies (3,29).

A significant influence of the amount smoked and age on lung cancer risk was confirmed in our study, even in the

NLST population with a relatively high minimum age of 55 years and a minimum smoking amount of 30 pack-years. These two variables accounted for the greatest proportion of the variability in lung cancer status explained by the multivariate models. Sex appeared to have a complex role, with no univariate relationship to lung cancer status but borderline significance in the multivariate models. The reason for this is uncertain, but we note that previous studies have produced conflicting results in regard to sex as a risk factor for lung cancer (30). As in our study, an inverse relationship between body mass index and lung cancer has been found in other studies; as with sex, however, findings in regard to body mass index and lung cancer risk varied, possibly because of the confounding influence of smoking, obstructive lung disease, and malignancy on weight (31).

The significance of an association between an adult history of asthma and a lower frequency of lung cancer is uncertain. Researchers in most other studies have found a positive association between asthma and lung cancer (32), although some have found a negative association between lung cancer and asthma in women (29) or between hay fever (3) and lung cancer. Of potential relevance to our results is that NLST data collection made an additional distinction between childhood and adult asthma that was not specified in prior studies. Biologically plausible arguments related both to the potential

carcinogenic effects of chronic inflammation and potential protective effects of increased immune surveillance in atopic conditions have been proposed, and the relationship between atopy and lung cancer remains controversial (32). Despite the known synergy between smoking and asbestos in lung cancer risk (33), we found no difference in lung cancer on the basis of reported occupational asbestos exposure. This finding could be because the theory linking asbestos to lung cancer through asbestosis (34) is correct, although there is strong disagreement (33), because there were few patients with a diagnosis of asbestosis, and we found no association between asbestosis and lung cancer. Alternatively, the low number of individuals with a long duration of asbestos exposure may have reduced the sensitivity for detecting a relationship. Because our study was designed to evaluate the contribution of CT emphysema and airway measurements to lung cancer risk assessment, we did not pursue these nonimaging risk factor relationships further in this study.

We note several limitations of our analyses. First, our results were based on a median follow-up interval of 6.6 years and may have been different with shorter or longer follow-up. However, omission from final data analysis of those who developed lung cancer after our initial case selection but before final analysis did not alter the results. Because emphysema (and possibly airway) measurements may vary with different scanners, section thicknesses, and reconstruction kernels (17,19,35), the absolute quantitative CT measurements represent an average from all such technical combinations in the study sample and may differ for individual scanners and techniques. However, matching on these parameters during case selection should have controlled for any unintended bias related to these technical factors. Lacking spirometry measurements, we are unable to determine whether the CT airway measurements were correlated with airflow obstruction or whether airflow obstruction was associated with lung cancer in this population. We cannot exclude the possibility

that a relationship between airway dimensions and lung cancer would be found if other bronchial segments also were assessed by using three-dimensional scanning and analytic techniques, although our results suggest that it is unlikely. More important, our study was not designed to develop a comprehensive lung cancer risk model; this goal and further investigation of associations between lung cancer and other clinical data collected would be best performed by means of an analysis of the entire NLST population.

In conclusion, although a significant association between quantitative emphysema measurements and lung cancer was found, the relationship was too weak to suggest that obtaining such measurements would be of any practical value for stratifying risk in a screening population of older, heavy smokers already at high risk for lung cancer. In addition, multivariate analyses showed that the addition of quantitative emphysema measurements to prediction models that are based on demographic and history factors readily obtainable by means of interview did not improve risk estimation. Airway dimensions were not associated with the occurrence of lung cancer.

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