

# Quantitative Computed Tomography Analysis, Airflow Obstruction, and Lung Cancer in the Pittsburgh Lung Screening Study

David O. Wilson, MD, MPH,\* Joseph K. Leader, PhD,† Carl R. Fuhrman, MD,† John J. Reilly, MD,\* Frank C. Sciurba, MD,\* and Joel L. Weissfeld, MD‡

**Background:** To study the relationship between emphysema, airflow obstruction, and lung cancer in a high-risk population, we performed quantitative analysis of screening computed tomography (CT) scans.

**Methods:** Subjects completed questionnaires, spirometry, and low-dose helical chest CT. Analyses compared cases and controls according to automated quantitative analysis of lung parenchyma and airways measures.

**Results:** Our case-control study of 117 matched pairs of lung cancer cases and controls did not reveal any airway or lung parenchymal findings on quantitative analysis of screening CT scans that were associated with increased lung cancer risk. Airway measures including wall area %, lumen perimeter, lumen area and average wall Hounsfield unit, and parenchymal measures including lung fraction less than  $-910$  Hounsfield units were not statistically different between cases and controls.

**Conclusions:** The relationship between visual assessment of emphysema and increased lung cancer risk could not be verified by quantitative analysis of low-dose screening CT scans in a high-risk tobacco exposed population.

**Key Words:** Emphysema, Airflow obstruction, Lung cancer risk.

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There is an association between airflow obstruction on spirometry and anatomic emphysema by visual assessment on low-dose screening computed tomography (CT) scan and lung cancer, as reported by us<sup>1</sup> and others.<sup>2–7</sup> Two reports from the Mayo Clinic lung cancer screening study with small numbers of lung cancers ( $n = 24$  and  $n = 64$ , respectively) used quantitative CT analysis to determine % emphysema and concluded that the quantity of radiographic emphysema

was not found to be a significant risk for lung cancer.<sup>8,9</sup> We report on 117 pairs of subjects with lung cancer and matched controls from the Pittsburgh Lung Screening Study (PLuSS) analyzed by quantitative CT analysis for airway and parenchymal abnormalities. This is the first study to correlate quantitative CT measures of parenchymal disease (lung fraction  $< -910$  Hounsfield unit [HU]) with visual emphysema, measures of airways disease (wall area and lumen measures) with forced expiratory volume in 1 second (FEV1), and lung cancer risk.

## METHODS

### Participants

The PLuSS involved 3642 subjects<sup>10</sup> and was approved by the Institutional Review Board of the University of Pittsburgh (approval no. 011171). Written informed consent was obtained from all participants. Between January 2002 and April 2005, volunteers with the following characteristics were recruited: (1) age 50 to 79 years; (2) no personal lung cancer history; (3) no participation in concurrent lung cancer screening studies; (4) no chest CT within 12 months; (5) current or ex-cigarette smoker of at least one-half pack per day for at least 25 years, and, if quit, quit for no more than 10 years before study enrollment; and (6) body weight less than 400 pounds. Individuals were not excluded because of symptoms.

PLuSS participants performed the following baseline activities (T0) between March 2002 and September 2005: (1) completed a risk factor questionnaire, (2) provided peripheral blood samples, (3) underwent forced expiratory spirometry conducted and analyzed in accordance with American Thoracic Society standards,<sup>11</sup> and (4) underwent low-dose screening CT examination and physician referral for noncalcified lung nodules. Follow-up activities (T1) were performed between March 2002 and November 2006 and included repeat low-dose screening CT examination after 12 months and active surveillance for lung cancer-related endpoints. This study includes 234 subjects selected from the PLuSS cohort, including 117 pathologically verified lung cancers and 117 control subjects, CT-screened lung cancer-free PLuSS subjects individually matched to the case group according to sex (men, women), year of birth category (before 1934, 1934–1943, and after 1943), year of baseline CT screening exam-

\*Division of Pulmonary, Allergy and Critical Care Medicine, Department of Medicine, †Department of Radiology, and ‡Department of Epidemiology, University of Pittsburgh, Pittsburgh, Pennsylvania.

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Address for correspondence: David O. Wilson, MD, MPH, UPMC-Shadyside Place, 580 S. Aiken Ave., Suite 400, Pittsburgh, PA 15232. E-mail: wilsondo@upmc.edu

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**TABLE 1.** Risk Factors, Cancer Cases vs. Matched Control Cases

Attribute	Cancers ( <i>n</i> = 117)		Controls <sup>a</sup> ( <i>n</i> = 117)		OR	95% CI	<i>p</i>
	<i>N</i>	Percentage	<i>N</i>	Percentage			
Sex <sup>b</sup>							
Men	61	52.1	61	52.1			
Women	56	47.9	56	47.9			
Age (yr)							
50–59	35	29.9	37	31.6			
60–69	57	48.7	56	47.9			
70+	25	21.4	24	20.5			
Race							
White	111	94.9	110	94.0			
Black	6	5.1	7	6.0			
Smoking status <sup>b</sup>							
Current or quit <3 yr	96	82.1	96	82.1			
Quit ≥3 yr	21	17.9	21	17.9			
Cigarette dose-duration index (pack years) <sup>b</sup>							
<40	27	23.1	27	23.1			
40–79	66	56.4	66	56.4			
80+	24	20.5	24	20.5			
Family history of cancer							
None or skin only	38	32.5	46	39.3	REF		0.04
Nonlung	49	41.9	56	47.9	1.05	0.59–1.85	
Lung only	13	11.1	12	10.3	1.36	0.56–3.34	
Lung + nonlung	17	14.5	3	2.6	6.43	1.78–23.2	
Visual emphysema							
None	31	26.5	64	54.7	REF		<.0001
Trace	28	23.9	24	20.5	2.64	1.28–5.44	
Mild	40	34.2	15	12.8	6.29	2.86–13.9	
Moderate-severe	18	15.4	14	12.0	3.02	1.27–7.18	
Airflow obstruction							
None	39	33.3	56	47.9	REF		0.12
GOLD I	20	17.1	17	14.5	1.82	0.84–3.96	
GOLD II	43	36.8	34	29.1	2.03	1.04–3.93	
GOLD III-IV	15	12.8	10	8.5	2.33	0.93–5.82	

<sup>a</sup> Includes two subjects with lung cancer diagnosed during extended follow-up.

<sup>b</sup> Factor used to match cases and controls.

ination (2002, 2003, 2004, and 2005), cigarette smoking status at time of PLuSS entry (current smokers and quit within 3 years, quit for more than 3 years), and pack-year smoking category (<40.0, 40–79.9, and 80.0+ pack-years).

### CT Examinations

The initial or prevalence (T0) lung cancer screening CT examinations was used for analysis in this study. The CT examinations were performed on a GE LightSpeed Plus 4-detector (*n* = 105) or GE LightSpeed Ultra 8-detector (*n* = 129) (GE Healthcare, Waukesha, WI) with the subjects holding their breath at end inspiration. The CT acquisition protocol was a noncontrasted, helical technique at 120 kVp (*n* = 45) or 140 kVp (*n* = 189), mean 24.4 (±8.3) mAs, and a HS (GE HealthCare “High Speed”) or 1.35:1 pitch. The CT images were contiguous and reconstructed at 2.5 mm thickness using the GE’s “lung” reconstruction kernel with a 512 × 512 pixel matrix.

### CT Examination Review

Readers used lung windows/level settings (1496/-555) to view images (2.5 mm section thickness) on a PACS monitor display system (Stentor; Radiology Informatics Business Group of Philips Medical Systems, Foster City, CA) and visually assessed the presence or absence of emphysema on a four-point scale as: (0) none, (1) trace, (2) mild, and (3) or (4) moderate-severe. The rating scale was based on a modified NETT rating that assigned using the percentages of emphysema: 0%, none; 1–10%, trace; 11–25%, mild; or 26% or greater moderate-severe.<sup>12</sup> Details, including measures of inter-reader reliability, appear in the online supplement to reference 1 (<http://ajrccm.atsjournals.org/cgi/data/178/7/738/DC1/1>).

### Quantitative CT Analysis

Lung regions depicted on each CT image were segmented from the surrounding chest wall and mediastinal

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