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Systematic Reviews and Meta- and Pooled Analyses

Previous Lung Diseases and Lung Cancer Risk: A Pooled Analysis From the International Lung Cancer Consortium

Darren R. Brenner, Paolo Boffetta, Eric J. Duell, Heike Bickeböller, Albert Rosenberger, Valerie McCormack, Joshua E. Muscat, Ping Yang, H.-Erich Wichmann, Irene Brueske-Hohlfeld, Ann G. Schwartz, Michele L. Cote, Anne Tjønneland, Søren Friis, Loic Le Marchand, Zuo-Feng Zhang, Hal Morgenstern, Neonila Szeszenia-Dabrowska, Jolanta Lissowska, David Zaridze, Peter Rudnai, Eleonora Fabianova, Lenka Foretova, Vladimir Janout, Vladimir Bencko, Miriam Schejbalova, Paul Brennan, Ioan N. Mates, Philip Lazarus, John K. Field, Olaide Raji, John R. McLaughlin, Geoffrey Liu, John Wiencke, Monica Neri, Donatella Ugolini, Angeline S. Andrew, Qing Lan, Wei Hu, Irene Orlow, Bernard J. Park, and Rayjean J. Hung*

* Correspondence to Dr. Rayjean J. Hung, Samuel Lunenfeld Research Institute, Mount Sinai Hospital, 60 Murray Street, Toronto, Ontario M5T 3L9, Canada (e-mail: rayjean.hung@lunenfeld.ca).

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To clarify the role of previous lung diseases (chronic bronchitis, emphysema, pneumonia, and tuberculosis) in the development of lung cancer, the authors conducted a pooled analysis of studies in the International Lung Cancer Consortium. Seventeen studies including 24,607 cases and 81,829 controls (noncases), mainly conducted in Europe and North America, were included (1984–2011). Using self-reported data on previous diagnoses of lung diseases, the authors derived study-specific effect estimates by means of logistic regression models or Cox proportional hazards models adjusted for age, sex, and cumulative tobacco smoking. Estimates were pooled using random-effects models. Analyses stratified by smoking status and histology were also conducted. A history of emphysema conferred a 2.44-fold increased risk of lung cancer (95% confidence interval (CI): 1.64, 3.62 (16 studies)). A history of chronic bronchitis conferred a relative risk of 1.47 (95% CI: 1.29, 1.68 (13 studies)). Tuberculosis (relative risk = 1.48, 95% CI: 1.17, 1.87 (16 studies)) and pneumonia (relative risk = 1.57, 95% CI: 1.22, 2.01 (12 studies)) were also associated with lung cancer risk. Among never smokers, elevated risks were observed for emphysema, pneumonia, and tuberculosis. These results suggest that previous lung diseases influence lung cancer risk independently of tobacco use and that these diseases are important for assessing individual risk.

bronchitis, chronic; emphysema; lung diseases; lung neoplasms; meta-analysis; pneumonia; pulmonary disease, chronic obstructive; tuberculosis

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; RR, relative risk.

Lung cancer continues to be the leading cause of cancer incidence and mortality worldwide, with an estimated 1,608,800 new cases and 1,378,400 deaths in 2008 (1). Disease survival remains dismal, with 5-year survival rates of approximately 15% among developed populations (2, 3). Although tobacco smoking continues to be the primary determinant of risk, further investigation is required concerning the additional risk factors for lung cancer, particularly among never smokers (4). One particular set of risk factors that may play an important role in lung cancer development is previous lung diseases. Recent evidence suggests that inflammatory processes may play a central role in carcinogenesis (5–8).

Previous lung diseases such as chronic obstructive pulmonary disease (COPD) (including emphysema and chronic bronchitis), pneumonia, and tuberculosis are major

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sources of inflammation in lung tissue (9, 10). The resulting inflammation has been suggested to increase the risk of lung cancer (11–13), and these diseases may act as catalysts in the development of lung neoplasms (14, 15). The associations between COPD (emphysema and/or chronic bronchitis), pneumonia, and tuberculosis and lung cancer have been investigated previously; however, a recent meta-analysis of the literature showed that most of the studies were small-scale initiatives—65% were identified as having fewer than 500 cases (16). In addition, the meta-analysis was not able to address the issues of standardized covariate adjustment, and data on never smokers and histologic type were limited. To address these limitations, we conducted a pooled analysis using primary data from 17 studies included in the International Lung Cancer Consortium to examine the risk of lung cancer associated with previous lung diseases.

MATERIALS AND METHODS

Data collection

Requirements for inclusion of studies in the International Lung Cancer Consortium and other details have been previously published (17) and are available on the Consortium's website (http://ilcco.iarc.fr). Investigators from 17 participating studies (out of 52 studies included in the

Table 1. Characteristics of Participating Studies in a Pooled Analysis of Previous Lung Diseases and Lung Cancer Risk, International Lung Cancer Consortium, 1984–2011

Continent and Study/Center	Principal Investigator	Control Source	Study Period	Location	No. of Cases	No. of Controls	Total No.
North America							
Family Health Study (WSU/KCI-1) (22)	A. G. Schwartz	Population	1984–2004	Detroit, Michigan, US	1,006	1,184	2,190
Study of women's lung cancer epidemiology (WSU/KCI-2) (30)	A. G. Schwartz	Population	2001–2007	Detroit, Michigan, US	576	575	1,151
University of California, Los Angeles (21)	Z. F. Zhang	Population	1999–2004	Los Angeles, California, US	611	1,040	1,651
New England Lung Cancer Study (25)	E. Duell	Population	2005–2008	New Hampshire, US	277	251	528
Samuel Lunenfeld Research Institute (18)	J. McLaughlin	Mixed	1997–2002	Toronto, Ontario, Canada	445	947	1,392
Mayo Clinic (27)	P. Yang	Mixed	1997–2006	Rochester, Minnesota, US	5,700	2,269	7,969
New York Multicenter Study (26)	J. Muscat	Hospital	1969–1999	New York State, US	5,130	4,942	10,072
Moffitt Cancer Study (24)	P. Lazarus	Hospital	1999–2003	Florida, US	497	898	1,395
University of California, San Francisco (29)	J. Wiencke	Population	1999–2002	San Francisco, California, US	428	900	1,328
Memorial Sloan-Kettering Cancer Center (33)	I. Orlow	Hospital	2003–2005	New York City, US	102	101	203
Hawaii (28)	L. Le Marchand	Population	1992–1997	Hawaii, US	635	588	1,223
Europe							
Liverpool Lung Project (35)	J. K. Field	Population	1998–2006	Liverpool, United Kingdom	475	954	1,429
CREST Biorepository (19)	M. Neri	Mixed	1996–ongoing	Genova, Italy	413	555	968
Helmholtz Center Munich (39, 40, 69, 70)	E. Wichmann	Population	2000–2004	Germany	4,735	8,178	12,913
Central Europe (23)	P. Boffetta	Hospital	1998–2002	Central/Eastern Europe	2,633	2,702	5,335
Danish Diet, Cancer, and Health Study[a] (20)	A. Tjønneland	Population-based cohort	1993–2009	Copenhagen, Denmark	822	55,623	56,445
Asia							
NCI-China (34)	Q. Lan	Population	1985–1990	Xuan Wei, People's Republic of China	122	122	244
Total					24,607	81,829	106,436

Abbreviations: CREST, Cancer of the Respiratory Tract; KCI, Karmanos Cancer Institute; NCI, National Cancer Institute; US, United States; WSU, Wayne State University.

[a] Population-based cohort included in counts as cases and controls.

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Consortium) contributed data on previous lung diseases and agreed to participate in this pooled analysis (Table 1). There was 1 population-based cohort study and 16 case-control studies, of which 9 were population-based, 4 were hospital-based, and 3 had mixed controls (where both population and hospital-based controls were sampled). Eleven studies were conducted in North America, 5 in Europe, and 1 in China; the dates of the studies ranged from 1984 to 2011. The control groups in all of the case-control studies were, at a minimum, frequency-matched with cases on age and sex. Written informed consent was obtained from all study subjects, and ethics review boards at each study center approved the study protocols. The data submitted from all 17 studies were checked for missing values, inadmissible values, aberrant distributions, and inconsistencies. Queries were sent to the investigators to resolve all discrepancies and possible errors. Subjects with unknown age or sex were excluded from the analysis ($n = 6$). A total of 24,607 cases and 81,829 controls were available for the present investigation.

Previous lung diseases were based on self-reported status of being previously diagnosed with chronic bronchitis, emphysema, pneumonia, or tuberculosis by a physician. Two of the studies asked open-ended questions about previous lung diseases, where responses were recorded using free text (18) or were coded using *International Classification of Diseases*, Ninth Revision, codes (19). Dichotomous variables were created for each of the previous lung diseases. Several studies also recorded the date of diagnosis of the disease (18, 20–28). Detailed descriptions of the 17 study populations within this analysis have been published elsewhere (18–34). Four of the studies had previously reported effect estimates for prior lung diseases (18, 25, 30, 35) and were included in the previous meta-analysis (16), whereas the other 13 studies (88% of the pooled study population) represented new data and were not included in the previous meta-analysis (Table 1).

Statistical methods

The frequency distributions of demographic variables and putative risk factors for lung cancer, including age, sex, ethnicity, and smoking, were examined among cases and controls combined. The ethnicity of the subjects was categorized according to the National Institutes of Health definition as non-Hispanic white, black or African-American, Hispanic or Latino, Asian, Native Hawaiian or Pacific Islander, American Indian, or other. Former smokers were defined as smokers who had quit smoking at least 2 years before the interview or diagnosis. Never smokers were defined as persons who had smoked fewer than 100 cigarettes over their lifetime. Cumulative tobacco smoking was calculated as the product of smoking duration and intensity throughout the life course, standardized across studies and expressed as pack-years.

For those studies that recorded the date of lung disease diagnosis, indicator variables for whether the diagnosis had been made 5 years or 10 years before the date of cancer diagnosis or control interview were created. For case-control studies, we estimated odds ratios and their associated 95% confidence intervals for the relation of each previous lung disease with lung cancer, using unconditional logistic regression, adjusting for age, sex, cumulative tobacco smoking (in pack-years), and country (when the study participants were from multiple countries). For the cohort study (20), we used Cox regression (with time since study entry as the time scale) to estimate hazard ratios, adjusted for age, sex, and pack-years, and their associated 95% confidence intervals for each previous lung disease. Follow-up time at risk was calculated as the time between study entry and lung cancer diagnosis (for cases) or the last known date of query (for noncases) from the cancer registry. Although we estimated hazard ratios or odds ratios across study sites, we refer to all effect estimates henceforth as relative risks for consistency.

When information on cumulative tobacco smoking was missing (<1%), it was imputed using the median of the study-specific control population for the smoking group (never/former/current) of the individual. We estimated pooled effects across studies, employing random-effects models to account for variability between study populations. Studies in which the odds ratio could not be estimated because of small numbers in one or more of the 4 categories in the 2×2 table of case-control status and history of previous lung diseases were omitted. We conducted an analysis stratified by smoking status to investigate the potential modifying effects of smoking or differential etiology across smoking groups. We also compared effect estimates across histologic subtypes to search for differential effects. We adjusted estimates for other lung diseases; however, since not all studies collected data for all diseases, this limited the sample in which we could conduct such an analysis. Subgroup analyses for large cell carcinoma are omitted from the results because there were very small numbers of cases in most studies and risk measures could not be estimated across studies unless data were pooled as a single study. We estimated population attributable fractions for each of the previous lung diseases based on the pooled adjusted effect estimates and the proportion of exposed persons among the cases (36).

Heterogeneity was evaluated for each of the summary estimates based on a test of the Cochrane Q statistic as well as the I^2 statistic (37). Where there was evidence of heterogeneity across studies, we evaluated the source of heterogeneity by means of meta-regression using control type, prevalence of ever smoking among controls, median year of the study period, and continents as predictors. If the heterogeneity could not be accounted for by the different study characteristics, we conducted an influence analysis to evaluate the source of heterogeneity from single studies using Galbraith plots (38) and Q statistics through an iterative process. Statistical analyses were conducted using SAS, version 9.1 (SAS Institute Inc., Cary, North Carolina), and STATA, version 10 (StataCorp LP, College Station, Texas).

RESULTS

The demographic distribution of the pooled data set for previous lung diseases is displayed in Table 2. The

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Table 2. Demographic Characteristics of Participants in a Pooled Analysis of Previous Lung Diseases and Lung Cancer Risk, International Lung Cancer Consortium, 1984–2011

	Cases ($n = 24,607$)			Controls (Noncases) ($n = 81,829$)		
	No.	%	Mean (SD)	No.	%	Mean (SD)
Age at diagnosis[a], years			61.1 (10.9)			56.4 (8.1)
Age group, years						
<50	4,434	18.0		12,135	14.8	
51–60	6,713	27.3		46,522	56.9	
61–70	8,392	34.1		19,156	23.4	
>70	5,068	20.6		4,016	4.9	
Sex						
Male	15,394	62.6		41,964	51.3	
Female	9,213	37.4		39,865	48.7	
Ethnicity						
White/Caucasian	21,030	85.5		74,890	91.5	
Black/African-American	1,379	5.6		1,698	2.1	
Asian	561	2.3		574	0.7	
Hispanic/Latino	313	1.3		629	0.8	
Other/unknown	1,324	5.4		4,038	4.9	
Smoking status						
Never smoker	2,719	11.0		29,884	36.5	
Ever smoker	21,888	88.9		51,945	63.5	
Former smoker	13,113	53.3		27,022	52.0	
Current smoker	8,775	35.7		24,923	48.0	
Pack-years of smoking[b]			44.1 (28.0)			28 (16.8)
<15	5,191	21.1		41,719	51.0	
15–<30	4,383	17.8		13,477	16.5	
30–45	6,179	25.1		21,168	25.9	
>45	8,854	36.0		5,465	6.7	
Histologic type[c]						
Adenocarcinoma	6,684	27.1				
Squamous cell carcinoma	4,685	19.0				
Small cell lung cancer	1,810	7.4				
Large cell lung cancer	824	3.3				

Abbreviation: SD, standard deviation.
[a] Age at baseline in the cohort study.
[b] Among ever smokers only.
[c] The remaining cases had either mixed or other histologic types.

majority of cases were Caucasian, male, and over the age of 60 years. As expected, there was a much higher proportion of never smokers among the controls. Adenocarcinoma and squamous cell carcinoma were the most commonly characterized histologic subtypes among cases in the pooled population. The prevalences of the 4 lung diseases examined among cases and controls across studies/centers, smoking groups, and histology groups are shown in Table 3.

Overall, all of the 4 previous lung diseases examined were associated with increased incidence of lung cancer when adjusted estimates were examined individually. Specifically, a previous diagnosis of emphysema was associated with increased risk overall, based on 16 studies (relative risk (RR) = 2.44, 95% confidence interval (CI): 1.64, 3.62; $I^2 = 89.37\%$), and when stratified according to never (RR = 2.21, 95% CI: 1.00, 4.90; $I^2 = 88.52\%$) or ever (RR = 2.25, 95% CI: 1.50, 3.37; $I^2 = 44.28$) smoking. The study-specific estimates, as well as estimates for subgroups of smoking status and histology, are shown in Figure 1. There was evidence of heterogeneity across studies that was not clearly explained by a single source (i.e., control type, proportion of ever smokers, time period, continent—all contributed ($P < 0.001$)). When we removed the outlying

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Table 3. Prevalence of Previous Lung Disease Among Lung Cancer Cases and Controls, by Study/Center, Smoking Status, and Histologic Type, International Lung Cancer Consortium, 1984–2011

	Emphysema				Chronic Bronchitis				Tuberculosis				Pneumonia			
	No. of Cases		No. of Controls		No. of Cases		No. of Controls		No. of Cases		No. of Controls		No. of Cases		No. of Controls	
	Exp.	Unexp.	Exp.	Unexp.	Exp.	Unexp.	Exp.	Unexp.	Exp.	Unexp.	Exp.	Unexp.	Exp.	Unexp.	Exp.	Unexp.
Study/center																
UCLA (21)	71	540	7	1,033	71	540	59	981	28	583	25	1,015	213	398	197	843
Helmholtz Center Munich (39, 40, 69, 70)	125	4,564	88	4,528	929	3,759	665	6,263	192	4,505	204	4,399	1,098	3,557	781	3,808
Central Europe (23)	75	2,552	47	2,652					207	2,420	150	2,550	900	1,727	689	2,009
NCI-China (34)	10	111	2	119	38	84	34	87	12	110	1	119				
Family Health Study (WSU/KCI-1) (22)	30	967	18	1,164	29	388	28	441	24	975	12	1,171	174	819	171	1,011
Study of women's lung cancer epidemiology (WSU/KCI-2) (30)	87	488	12	560	123	450	65	507	19	551	16	555	207	365	187	384
Hawaii (28)	105	525	20	568	36	593	15	573	26	605	28	560				
Samuel Lunenfeld Research Institute (18)	31	270	8	436	21	424	49	898	6	439	5	942	11	434	35	912
Liverpool Lung Project (35)	6	317	31	875					9	314	40	865	41	282	138	768
Mayo Clinic (27)	1,167	4,533	36	2,233					63	5,637	18	2,251	897	4,803	123	2,146
New England Lung Cancer Study (25)	46	228	10	241	41	235	13	238	3	272	2	249	123	152	73	178
Moffitt Cancer Study (24)	67	428	29	861	55	440	36	853								
New York Multicenter Study (26)	299	4,831	82	4,860	527	4,603	201	4,741	50	5,080	29	4,913				
CREST Biorepository (19)	10	403	4	551	77	336	14	541	7	406	3	552	21	392	14	541
UCSF (29)	77	349	45	853					20	407	19	881	168	258	167	733
MSKCC (33)					6	90	4	96	4	90	1	97				
Danish Diet, Cancer, and Health Study (20)	15	807	271	55,352	45	777	1022	54,601	6	816	108	55,515	242	580	4,154	51,469
Smoking status																
Never smoker	44	2,514	94	28,007	90	1,516	459	26,312	70	2,588	208	27,883	343	1,848	1,852	24,018
Ever smoker	2,177	19,399	616	48,879	1,908	11,203	1,746	44,508	606	20,622	453	48,751	3,752	11,919	4,877	40,784
Former smoker	1,644	11,312	335	25,576	1,203	5,988	821	22,655	334	12,426	298	25,403	2,240	8,262	2,292	21,141
Current smoker	533	8,087	281	23,303	705	5,215	925	21,853	272	8,196	155	23,348	1,512	3,657	2,585	19,643
Histologic type																
Adenocarcinoma	705	5,551			277	2,792			159	6,287			950	3,933		
Squamous cell carcinoma	588	3,847			226	1,689			127	4,270			839	2,340		
Small cell lung cancer	175	1,607			62	618			50	1,700			301	1,098		
Total	2,221	21,913	710	76,886	1,998	12,719	2,205	70,820	676	23,210	661	76,634	4,095	13,767	6,729	64,802
With removal(s)[a]	769	9,028	498	65,641					453	18,044	440	71,561	2,602	7,432	2,033	9,061

Abbreviations: CREST, Cancer of the Respiratory Tract; Exp., exposed; KCI, Karmanos Cancer Institute; MSKCC, Memorial Sloan-Kettering Cancer Center; UCLA, University of California, Los Angeles; UCSF, University of California, San Francisco; Unexp., unexposed; WSU, Wayne State University.

[a] Removal of one or more particular studies for each previous disease as specified in the figure legends.

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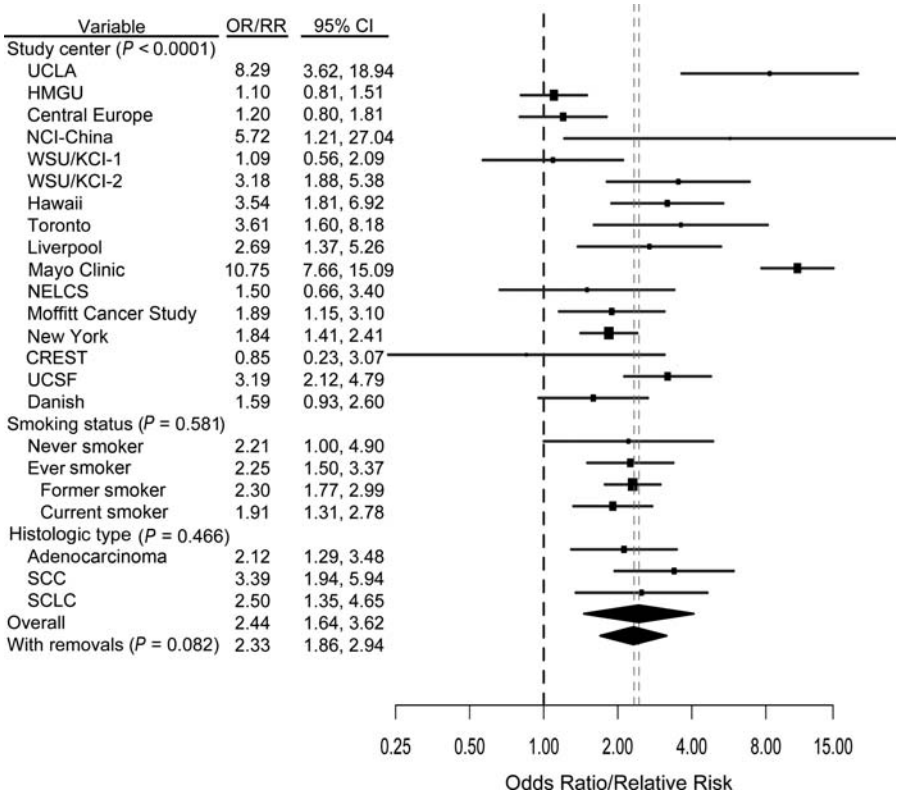

Figure 1. Results from a pooled analysis of emphysema as a risk factor for the development of lung cancer, International Lung Cancer Consortium, 1984–2011. The graph shows a forest plot of the association between emphysema and lung cancer risk by study center, smoking status, and histologic type. Models adjusted for age, sex, and pack-years of smoking. *P* values are from a test for heterogeneity across studies or across subgroups. "With removals" represents removal of the Mayo, Central Europe, HMGU, WSU/KCI-2, and UCLA studies. See Table 1 for published references. (CI, confidence interval; CREST, CREST (Cancer of the Respiratory Tract) Biorepository; Danish, Danish Diet, Cancer, and Health Study; HMGU, Helmholtz Center Munich; KCI, Karmanos Cancer Institute; Liverpool, Liverpool Lung Project; NCI, National Cancer Institute; NELCS, New England Lung Cancer Study; New York, New York Multicenter Study; OR, odds ratio; RR, relative risk; SCC, squamous cell carcinoma; SCLC, small cell lung cancer; Toronto, Samuel Lunenfeld Research Institute; UCLA, University of California, Los Angeles; UCSF, University of California, San Francisco; WSU, Wayne State University; WSU/KCI-1, Family Health Study; WSU/KCI-2, study of women's lung cancer epidemiology).

studies (21–23, 27, 39) as indicated by the Galbraith plot (see Web Figure 1 (http://aje.oxfordjournals.org/)), we observed marginal attenuation in the pooled effect estimate (RR = 2.33, 95% CI: 1.86, 2.94; $I^2 = 40.52\%$). After adjustment for other previous lung diseases, the relative risk associated with emphysema was 2.05 (95% CI: 1.33, 3.15; $I^2 = 89.95\%$) (data not shown).

A previous diagnosis of chronic bronchitis was associated with increased risk overall, based on 13 studies (RR = 1.47, 95% CI: 1.29, 1.68; $I^2 = 33.91\%$), and among ever smokers (RR = 1.63, 95% CI: 1.40, 1.89; $I^2 = 40.79\%$) (Figure 2). There was no evidence of heterogeneity across the 13 studies ($P = 0.111$). After adjustment for other previous lung diseases, the risk ratio for chronic bronchitis was 1.25 (95% CI: 1.05, 1.56; $I^2 = 60.70\%$) (data not shown). When the effects of chronic bronchitis and emphysema were examined as a measure of COPD, the combined overall effect of COPD was a relative risk of 1.93 (95% CI: 1.48, 4.89; $I^2 = 89.54\%$) (data not shown).

A previous diagnosis of pneumonia was associated with increased risk overall, based on 12 studies (RR = 1.57, 95% CI: 1.22, 2.01; $I^2 = 93.00\%$), and when stratified according to never (RR = 1.35, 95% CI: 1.12, 1.63; $I^2 = 23.01\%$) or ever (RR = 1.55, 95% CI: 1.16, 2.06; $I^2 = 93.18\%$) smoking (Figure 3). There was evidence of heterogeneity across studies that was not clearly explained by a single source ($P < 0.001$). When we removed the outlying studies (18, 20, 27, 29, 30) as indicated by the Galbraith plot (Web Figure 2), we observed a slight attenuation in the pooled effect estimate (RR = 1.39, 95% CI: 1.27, 1.52; $I^2 = 14.28\%$). After adjustment for other previous lung diseases, the relative risk for pneumonia was 1.42 (95% CI: 1.09, 1.86; $I^2 = 93.13\%$) (data not shown).

A previous diagnosis of tuberculosis was associated with increased risk overall, based on 16 studies (RR = 1.48, 95% CI: 1.17, 1.87; $I^2 = 54.27\%$), and among ever smokers (RR = 1.36, 95% CI: 1.05, 1.75; $I^2 = 47.96\%$) (Figure 4). We also observed an elevated risk among never smokers

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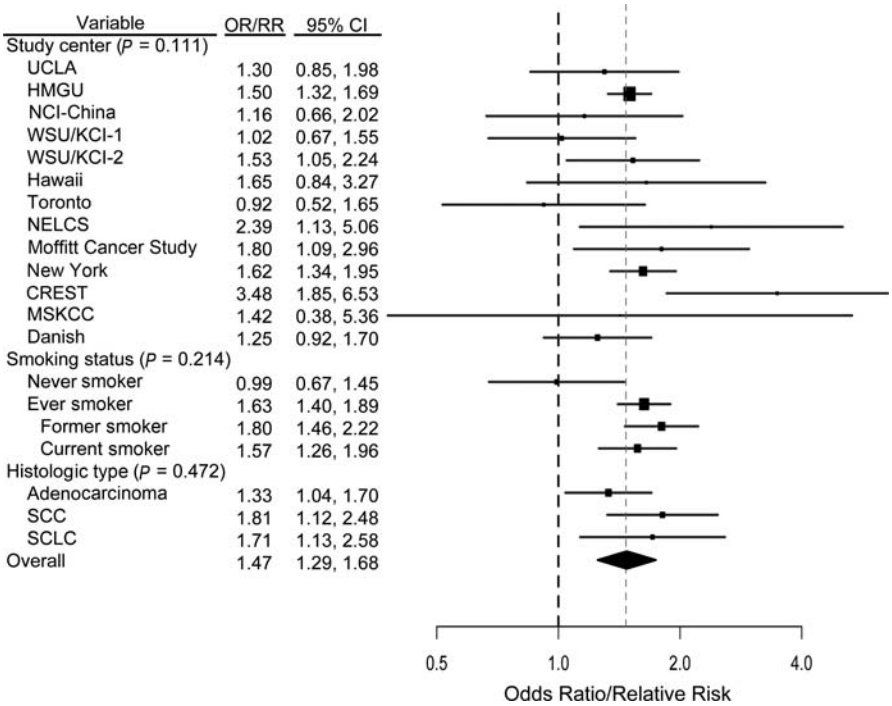

Figure 2. Results from a pooled analysis of chronic bronchitis as a risk factor for the development of lung cancer, International Lung Cancer Consortium, 1984–2011. The graph shows a forest plot of the association between chronic bronchitis and lung cancer risk by study center, smoking status, and histologic type. Models adjusted for age, sex, and pack-years of smoking. *P* values are from a test for heterogeneity across studies or across subgroups. (CI, confidence interval; CREST, CREST (Cancer of the Respiratory Tract) Biorepository; Danish, Danish Diet, Cancer, and Health Study; HMGU, Helmholtz Center Munich; KCI, Karmanos Cancer Institute; MSKCC, Memorial Sloan-Kettering Cancer Center; NELCS, New England Lung Cancer Study; New York, New York Multicenter Study; NCI, National Cancer Institute; OR, odds ratio; RR, relative risk; SCC, squamous cell carcinoma; SCLC, small cell lung cancer; Toronto, Samuel Lunenfeld Research Institute; UCLA, University of California, Los Angeles; WSU, Wayne State University; WSU/KCI-1, Family Health Study; WSU/KCI-2, study of women's lung cancer epidemiology).

(RR = 1.50, 95% CI: 1.03, 2.19; $I^2 = 23.64\%$). There was evidence of heterogeneity across studies ($P = 0.005$); however, when we examined the Galbraith plot, it appeared that the heterogeneity was due to only 1 outlying study (40) (Web Figure 3). When this study was removed, a slight elevation in the pooled effect estimate was observed (RR = 1.56, 95% CI: 1.24, 1.96; $I^2 = 34.95\%$). After adjustment for other previous lung diseases, the relative risk for tuberculosis was 1.31 (95% CI: 1.03, 1.56; $I^2 = 50.99\%$) (data not shown).

In those studies where multiple diseases were investigated, we examined the risk associated with having multiple lung diseases. There was a dose-response relation with increasing number of previous lung diseases (P-trend < 0.001). The relative risk associated with having 1 disease was 1.71 (95% CI: 1.61, 1.82); with having 2 diseases, it was 2.00 (95% CI: 1.80, 2.21); with having 3 diseases, 2.23 (95% CI: 1.76, 2.82); and with having all 4 diseases, 2.44 (95% CI: 0.92, 6.48) (only 8 controls and 15 cases had had all 4 diseases). We examined the effects of all 4 lung diseases separately among males and females and observed no differential effects by sex. (Full subgroup analyses are shown in Web Table 1.)

Population attributable fraction estimates for the diseases investigated ranged within the combined population from 0.9% for tuberculosis to 8.3% for pneumonia, with study-specific estimates varying according to population disease prevalence (tuberculosis, 0.29%–9.76%; chronic bronchitis, 3.63%–30.28%; emphysema, 1.20%–17.90%; pneumonia, 0.51%–44.11%). Among never smokers as a combined group, having had any of the previous lung diseases of interest conferred an attributable fraction of 5.91% (Web Table 2).

DISCUSSION

In this investigation into the effects of previous lung diseases on lung cancer risk, we found associations with increased cancer risk for each of the diseases of interest. Comparisons among all histologic subgroups were consistent with increases in risk observed overall, with the exception of squamous cell carcinoma among persons with tuberculosis. Risk estimates were consistent across smoking subgroups; estimates were elevated in all subgroups, with the exception of chronic bronchitis. Our results among never smokers suggest an effect of previous lung diseases

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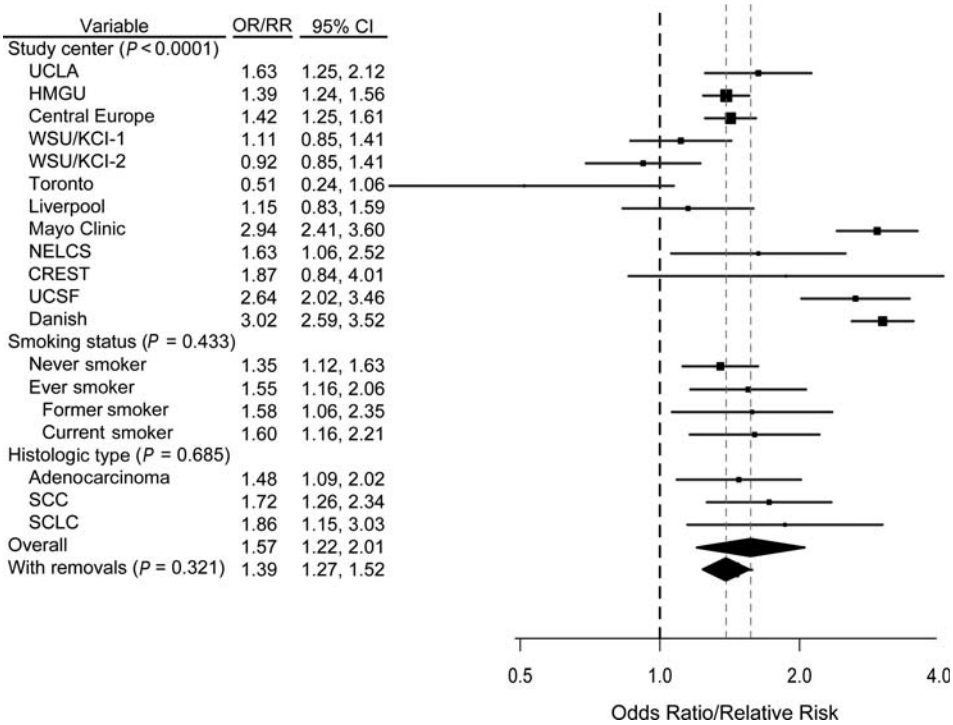

Figure 3. Results from a pooled analysis of pneumonia as a risk factor for the development of lung cancer, International Lung Cancer Consortium, 1984–2011. The graph shows a forest plot of the association between pneumonia and lung cancer risk by study center, smoking status, and histologic type. Models adjusted for age, sex, and pack-years of smoking. *P* values are from a test for heterogeneity across studies or across subgroups. "With removals" represents removal of the Toronto, WSU/KCI-2, UCSF, Mayo, and Danish studies. (CI, confidence interval; CREST, CREST (Cancer of the Respiratory Tract) Biorepository; Danish, Danish Diet, Cancer, and Health Study; HMGU, Helmholtz Center Munich; KCI, Karmanos Cancer Institute; Liverpool, Liverpool Lung Project; NELCS, New England Lung Cancer Study; OR, odds ratio; RR, relative risk; SCC, squamous cell carcinoma; SCLC, small cell lung cancer; Toronto, Samuel Lunenfeld Research Institute; UCLA, University of California, Los Angeles; UCSF, University of California, San Francisco; WSU, Wayne State University; WSU/KCI-1, Family Health Study; WSU/KCI-2, study of women's lung cancer epidemiology).

on lung cancer risk independent of tobacco smoking, probably acting through the inflammatory response and pathogenesis associated with the diseases.

The results of this pooled analysis corroborate the results of the previous meta-analysis suggesting that there was a large difference in the prevalence of COPD/emphysema among cases and controls (16). This difference in prevalence among cases and controls may explain/confound the differential effects observed in genetic epidemiologic studies of lung cancer in which inconsistent effects have been observed among populations of similar genetic ancestry (41) or may act as mediators in the associations between the variants and lung cancer risk (42). Although chronic bronchitis and emphysema are commonly grouped together as COPD, we calculated detailed results for each condition separately in order to allow for differential effects of these two conditions, which have different pathologies and etiologies. Because we observed independent effects of both of these diseases when adjusting for the other in a fixed-effects analysis, we felt this to be a beneficial approach.

Reverse causality and the issue of temporality are paramount to the consideration of causality for these associations. It is certainly possible that some of the conditions were early manifestations or symptoms of lung cancer that were misdiagnosed, particularly for emphysema and chronic bronchitis. For pneumonia and tuberculosis, infections may have been the result of a weakened immune system due to lung cancer. In addition, tumors may have been interpreted as lesions from infections prior to cancer diagnosis. To address these issues, we conducted a latency analysis which found that diagnoses of the previous lung diseases more than 5 years and more than 10 years prior to cancer diagnosis were positively associated with lung cancer incidence. This suggests that reverse causality is not likely to fully explain these associations. For example, when the analysis was restricted to the conditions diagnosed 10 years prior to lung cancer, chronic bronchitis remained associated with an increased risk of lung cancer (RR = 1.45, 95% CI: 1.08, 1.95). Complete results of latency analyses are available in Web Table 3. Note that in the cohort study included in this analysis (20), both lung disease and smoking status were ascertained at baseline and the average follow-up time to diagnosis/censoring was approximately 7 years.

The use of self-reports for measuring previous lung diseases may have introduced misclassification bias into the

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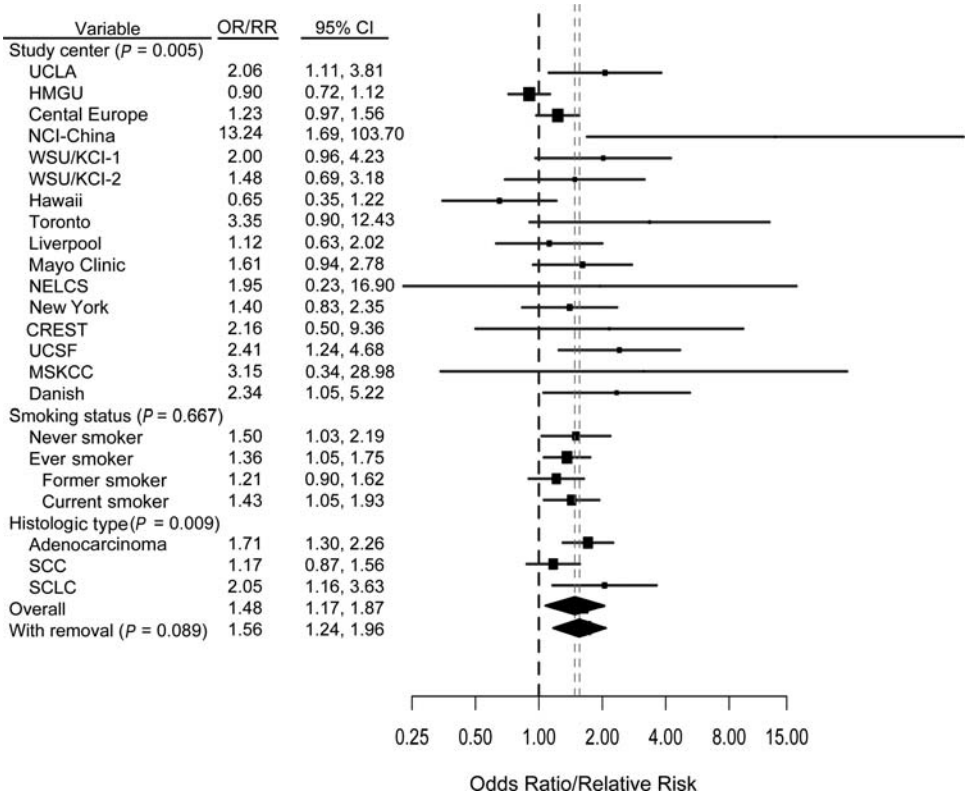

Figure 4. Results from a pooled analysis of tuberculosis as a risk factor for the development of lung cancer, International Lung Cancer Consortium, 1984–2011. The graph shows a forest plot of the association between tuberculosis and lung cancer risk by study center, smoking status, and histologic type. Models adjusted for age, sex, and pack-years of smoking. *P* values are from a test for heterogeneity across studies or across subgroups. "With removal" represents removal of the HMGU study. (CI, confidence interval; CREST, CREST (Cancer of the Respiratory Tract) Biorepository; Danish, Danish Diet, Cancer, and Health Study; HMGU, Helmholtz Center Munich; KCI, Karmanos Cancer Institute; Liverpool, Liverpool Lung Project; MSKCC, Memorial Sloan-Kettering Cancer Center; NCI, National Cancer Institute; NELCS, New England Lung Cancer Study; New York, New York Multicenter Study; OR, odds ratio; RR, relative risk; SCC, squamous cell carcinoma; SCLC, small cell lung cancer; Toronto, Samuel Lunenfeld Research Institute; UCLA, University of California, Los Angeles; UCSF, University of California, San Francisco; WSU, Wayne State University; WSU/KCI-1, Family Health Study; WSU/KCI-2, study of women's lung cancer epidemiology).

studies included in the pooled analysis. Quantitative techniques for each of the previous lung diseases are presently available for improved diagnostic accuracy and disease classification; however, these were not employed in any of the component studies of the analysis. When effect estimates obtained using quantitative diagnostic tools for COPD (forced expiratory volume in 1 second, quantitative computed tomography, or radiographic evidence), pneumonia (microimmunofluorescence), and tuberculosis (radiography) were pooled in the previous meta-analysis (16), the risk estimates derived using quantitative techniques were consistent with those derived using self-reported diagnoses. The similarity between effect estimates from the cohort study included in the analysis and the pooled case-control estimates (results not shown) suggests that potential bias due to misclassification of exposure, recall bias, and reverse causality may not explain the associations completely. Although none of the studies contained in this analysis validated self-reports with medical records, self-reported COPD has been shown to have a high level of agreement with spirometry results (43, 44). Despite the reports of these previous studies, misclassification of exposure may have produced underestimation of the burden due to the exposures, since several investigations have shown that COPD/emphysema is present in many lung cancer patients who do not report a history of COPD (45–47).

For pneumonia, the question of persistence of inflammation arising from a condition with clinical transience should be addressed. Because this investigation did not contain information on the number of infections or the length and/or intensity of infection, it is difficult to conceptually include pneumonia with the other diseases in terms of persistence of inflammation. However, murine models have suggested that infection from *Mycoplasma pneumoniae* can lead to long-term changes in peribronchial histopathology (48), pulmonary airflow resistance, and elevated inflammatory biomarkers long after active infection clears (49). This suggests that inflammation resulting from pneumonia may be

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more long-term in nature than clinical symptoms may suggest.

It is also possible that our results, particularly among never smokers, may have been confounded from exposure to other agents such as secondhand smoke or other occupational exposures. Secondhand smoke has been associated with increased risk of lung cancer (50) and may be related to previous lung diseases (51). However, it is unlikely to fully explain the large effects associated with several of the previous lung diseases. When we adjusted for secondhand smoke in our analysis among never smokers, the results remained, with risk estimates changing only slightly. For example, the relative risk associated with pneumonia among never smokers changed marginally from 1.35 to 1.45. In addition, occupational exposures may have acted as confounders in the associations tested, as they have been associated with lung cancer (52, 53). We examined the inclusion of restricted cubic splines to check for nonlinearity in both age and smoking (pack-years) as covariates in the association models. As was previously observed (54), nonlinear components for age and smoking were significant in the models, suggesting a deviation from linear fit; however, the effect estimates for the lung diseases pooled across studies changed minimally. Therefore, we retained linear terms in the models to avoid overdispersion in small studies when examining the within-study effects.

For those instances where heterogeneity was observed in the overall estimates (emphysema, pneumonia, tuberculosis), removal of the outlying studies led to only slight differences in the pooled estimates. For emphysema and pneumonia, where more than one study was contributing to heterogeneity, meta-regression suggested that several sources, including continent, control type, and proportion of ever smokers, all accounted for some portion of the heterogeneity (results not shown). In subgroup analyses where more than 3 studies were included in a pooled estimate, the only major difference was seen for emphysema between Europe and North America (Web Table 1). For emphysema, differences by continent of study may be a product of different diagnostic practices across populations, since diagnostic criteria for COPD differ across continents. More specifically, the diagnostic guidelines of the British Thoracic Society and the American Thoracic Society lead to marked differences in the prevalence of COPD when applied to the same population (55). Diagnostic differences across study locations that are not discernable from questionnaires may also explain some portion of the heterogeneity. Although these differences in diagnostic practice should produce nondifferential variation in disease status classification across cases and controls, the potential of this to influence the results should not be precluded. Several studies included in this analysis displayed COPD (emphysema/chronic bronchitis) prevalence higher than that in the community at large (Web Table 2), where it is often largely undiagnosed (56). For emphysema, control source contributed significantly to heterogeneity, suggesting that the differences in diagnosis in population-based settings compared with hospital-based settings may affect the prevalence of disease reported and therefore the magnitude of estimates and associated population attribution measures.

Strengths of this investigation include the large sample size and the large number of exposed persons. The use of random-effect models, although it provides wider confidence intervals, reduces the likelihood of larger studies' overly affecting pooled estimates when combining data across studies by estimating both within- and across-study variance. The inclusion of prospective data is also a strength of this pooled analysis, although the number of cases collected prospectively was comparatively smaller, whereby the biases associated with case-control studies could be comparatively evaluated.

In conclusion, we observed elevated lung cancer risks associated with previous diagnoses of emphysema, chronic bronchitis, pneumonia, and tuberculosis in this pooled analysis of primary data. The observation of relatively consistent associations between several of the previous lung diseases and lung cancer risk across smoking groups, histologic subtypes, and study designs supports a direct association with lung cancer, reducing the likelihood of confounding by tobacco exposure. The most likely explanation for the increased risk associated with these diseases is the effect of the inflammatory response within lung tissue. Recent evidence has suggested that inflammation plays a pivotal role in the development of lung cancer (12, 57, 58). Inflammation may increase the risk of cancer development as an initiator or promoter through 3 processes: increased genetic mutation, antiapoptotic signaling (59), and angiogenesis (14).

Whether acting as promoters in the causal pathway or as causative agents, these diseases appear to be markers of risk for the development of lung cancer that are clinically relevant. Most importantly, when considered as a group, the lung diseases examined in this pooled analysis affect large numbers of persons. In the United States, the prevalence of emphysema is 18.5 per 1,000 persons, and the prevalence of chronic bronchitis is 43.0 per 1,000 (60). Although the incidence of pneumonia in the United States is unknown, there were approximately 1.4 million hospital discharges associated with pneumonia in 2005 (61). While the incidence of tuberculosis in North America is low (4.8 per 100,000 population per year) (62), in developing nations the disease affects millions. In Europe and Asia, these conditions collectively affect millions of persons, and thus the exposed population is large (63). Therefore, the positive associations between the lung diseases examined and lung cancer risk are of substantial public health importance, and the consistent associations suggest that a nontrivial proportion of all lung cancer cases are attributable to these other lung diseases or their underlying pathologies.

The previous lung diseases examined in this investigation are significant for both public health and clinical practice. The development of lung cancer risk prediction models (54, 64, 65) should continue to incorporate the lung diseases examined in this analysis for improved discriminatory ability among all patients, regardless of smoking history. The United Kingdom Lung Cancer Screening Trial, which uses computed tomography to screen for lung cancer, utilizes the lung cancer risk prediction model of the Liverpool Lung Project, which includes pneumonia as one of the factors (62) for selection of high-risk individuals for the trial (66). These diseases may be useful in determining

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who to monitor by providing a further resolution of risk stratification, particularly as new-era screening evaluations and initiatives advance (67, 68).

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Author affiliations: Samuel Lunenfeld Research Institute, Mount Sinai Hospital, Toronto, Ontario, Canada (Darren R. Brenner, John R. McLaughlin, Rayjean J. Hung); Division of Epidemiology, Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada (Darren R. Brenner, John R. McLaughlin, Rayjean J. Hung); Institute for Translational Epidemiology, Mount Sinai School of Medicine, New York, New York (Paolo Boffetta); International Prevention Research Institute, Lyon, France (Paolo Boffetta); Unit of Nutrition, Environment and Cancer, Cancer Epidemiology Research Program, Catalan Institute of Oncology, Barcelona, Spain (Eric J. Duell); Department of Genetic Epidemiology, Medical School, Georg-August University of Göttingen, Göttingen, Germany (Heike Bickeböller, Albert Rosenberger); International Agency for Research on Cancer, Lyon, France (Valerie McCormack, Paul Brennan); Division of Epidemiology, Penn State Cancer Institute, Pennsylvania State University, State College, Pennsylvania (Joshua E. Muscat); Departments of Pharmacology and Health Evaluation Sciences, Penn State Cancer Institute, Pennsylvania State University, State College, Pennsylvania (Philip Lazarus); Epidemiology and Genetics of Lung Cancer Research Program, Mayo Clinic, Rochester, Minnesota (Ping Yang); Institute of Epidemiology, Helmholtz Center Munich, German Research Center for Environmental Health, Neuherberg, Germany (H.-Erich Wichmann, Irene Brueske-Hohlfeld); Department of Oncology, School of Medicine, Wayne State University, Detroit, Michigan (Ann G. Schwartz, Michele L. Cote); Karmanos Cancer Institute, Detroit, Michigan (Ann G. Schwartz, Michele L. Cote); Institute of Cancer Epidemiology, Danish Cancer Society, Copenhagen, Denmark (Anne Tjønneland, Søren Friis); University of Hawaii Cancer Center, Honolulu, Hawaii (Loic Le Marchand); Department of Epidemiology, School of Public Health, University of California, Los Angeles, Los Angeles, California (Zuo-Feng Zhang); Departments of Epidemiology and Environmental Health Sciences, School of Public Health, University of Michigan, Ann Arbor, Michigan (Hal Morgenstern); Comprehensive Cancer Center, University of Michigan, Ann Arbor, Michigan (Hal Morgenstern); Department of Epidemiology, Institute of Occupational Medicine, Lodz, Poland (Neonila Szeszenia-Dabrowska); Department of Cancer Epidemiology and Prevention, M. Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Warsaw, Poland (Jolanta Lissowska); Institute of Carcinogenesis, Cancer Research Centre, Moscow, Russia (David Zaridze); Fodor József National Center for Public Health, National Institute of Environmental Health, Budapest, Hungary (Peter Rudnai); Department of Occupational Health, Specialized State Health Institute, Banska Bystrica, Slovakia (Eleonora Fabianova); Department of Cancer Epidemiology and Genetics, Masaryk Memorial Cancer Institute, Brno, Czech Republic (Lenka Foretova); Department of Preventive Medicine, Faculty of Medicine, Palacky University, Olomouc, Czech Republic (Vladimir Janout); Institute of Hygiene and Epidemiology, First Faculty of Medicine, Charles University, Prague, Czech Republic (Vladimir Bencko, Miriam Schejbalova); University of Medicine and Pharmacy Carol Davila, Bucharest, Romania (Ioan N. Mates); Roy Castle Lung Cancer Research Programme, Department of Molecular and Clinical Cancer Medicine, University of Liverpool Cancer Research Centre, Liverpool, United Kingdom (John K. Field, Olaide Raji); Ontario Cancer Institute, Princess Margaret Hospital, Toronto, Ontario, Canada (Geoffrey Liu); Department of Epidemiology and Biostatistics, School of Medicine, University of California, San Francisco, San Francisco, California (John Wiencke); Unit of Clinical and Molecular Epidemiology, IRCCS (Istituto di Ricovero e Cura a Carattere Scientifico) San Raffaele Pisana, Rome, Italy (Monica Neri); Units of Epidemiology and Biostatistics, University of Genoa, Genoa, Italy (Donatella Ugolini); Units of Epidemiology, Biostatistics, and Clinical Trials, National Cancer Research Institute, Genoa, Italy (Donatella Ugolini); Unit of Biostatistics and Epidemiology, Department of Community and Family Medicine, Norris Cotton Cancer Center, Dartmouth Medical School, Lebanon, New Hampshire (Angeline S. Andrew); Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland (Qing Lan, Wei Hu); Department of Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, New York (Irene Orlow); and Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, New York (Bernard J. Park).

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