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Original Contribution

Lung Cancer and Occupation in a Population-based Case-Control Study

Dario Consonni*, Sara De Matteis, Jay H. Lubin, Sholom Wacholder, Margaret Tucker, Angela Cecilia Pesatori, Neil E. Caporaso, Pier Alberto Bertazzi, and Maria Teresa Landi

* Correspondence to Dr. Dario Consonni, Unit of Epidemiology, Department of Preventive Medicine, Fondazione IRCCS Ospedale Maggiore Policlinico, Mangiagalli e Regina Elena, Via San Barnaba, 8, 20122 Milano, Italy (e-mail: dario.consonni@unimi.it).

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The authors examined the relation between occupation and lung cancer in the large, population-based Environment And Genetics in Lung cancer Etiology (EAGLE) case-control study. In 2002–2005 in the Lombardy region of northern Italy, 2,100 incident lung cancer cases and 2,120 randomly selected population controls were enrolled. Lifetime occupational histories (industry and job title) were coded by using standard international classifications and were translated into occupations known (list A) or suspected (list B) to be associated with lung cancer. Smoking-adjusted odds ratios and 95% confidence intervals were calculated with logistic regression. For men, an increased risk was found for list A (177 exposed cases and 100 controls; odds ratio = 1.74, 95% confidence interval: 1.27, 2.38) and most occupations therein. No overall excess was found for list B with the exception of filling station attendants and bus and truck drivers (men) and launderers and dry cleaners (women). The authors estimated that 4.9% (95% confidence interval: 2.0, 7.8) of lung cancers in men were attributable to occupation. Among those in other occupations, risk excesses were found for metal workers, barbers and hairdressers, and other motor vehicle drivers. These results indicate that past exposure to occupational carcinogens remains an important determinant of lung cancer occurrence.

carcinogens; case-control studies; industry; lung neoplasms; occupational health; occupations

Abbreviations: CI, confidence interval; OR, odds ratio; PAF, population attributable fraction.

Lung cancer is the most frequent neoplasm worldwide, with more than 1.4 million new cases and 1.3 million deaths in 2004 (1). Rates for men have peaked in many areas of the world, but adenocarcinomas in both genders and all lung cancer types among women are still increasing (2). Although tobacco smoking is by large the most important cause, occupational factors play a remarkable role. In the year 2000, it was estimated that 10% of lung cancer deaths among men (88,000 deaths) and 5% among women (14,300 deaths) worldwide were attributable to exposure to 8 occupational lung carcinogens (arsenic, asbestos, beryllium, cadmium, chromium, diesel fumes, nickel, and silica) (3–5). In Europe, assuming attributable fractions of 7%–15% (men) and 2%–9% (women), the estimated numbers of deaths were more than 29,300 and 3,200, respectively (3). In the United States, using 1997 mortality data and attributable fractions of 6.1%–17.3% (men) and 2% (women), about 6,800–17,000 lung cancers (both genders) were estimated to be caused by exposure to chemicals in the workplace (6, 7).

Prevalence of occupational exposure to carcinogens is still high: in 1990–1993, of almost 140 million workers in 15 states of the European Union, 32 million were estimated to be exposed to carcinogenic agents and about 7 million to the 8 above-mentioned carcinogens (8). The corresponding estimates for Italy were more than 4 million and 1 million, respectively (9); 10 years later (2000–2003), only modest decreases were found (10).

Different approaches are used to evaluate occupational exposure to carcinogens (11–15): one makes use of lists of occupations known (list A) or suspected (list B) to be associated with lung cancer based on evaluations of

Table 1. Selected Characteristics of Lung Cancer Cases and Controls With Interview Data Available, the EAGLE Study, Lombardy, Italy, 2002–2005[a,b]

	Women				Men			
	Cases		Controls		Cases		Controls	
	No.	%	No.	%	No.	%	No.	%
Total participants enrolled	448		500		1,652		1,620	
Interviewed	406	100.0	499	100.0	1,537	100.0	1,617	100.0
Area of residence								
Milan	288	70.9	349	69.9	987	64.2	1,089	67.3
Monza	24	5.9	23	4.6	109	7.1	94	5.8
Brescia	47	11.6	53	10.6	203	13.2	194	12.0
Pavia	21	5.2	37	7.4	107	7.0	92	5.7
Varese	26	6.4	37	7.4	131	8.5	148	9.2
	$P = 0.55$				$P = 0.17$			
Age, years (mean (SD))	64.8 (10.1)		64.1 (10.1)		66.8 (7.9)		65.8 (8.1)	
	$P = 0.32$				$P < 0.001$			
Educational level								
None	21	5.2	24	4.8	91	5.9	66	4.1
Elementary school	128	31.5	143	28.7	625	40.7	431	26.7
Middle school	134	33.0	158	31.7	424	27.6	455	28.1
High school	104	25.6	135	27.1	314	20.4	441	27.3
University	19	4.7	39	7.8	83	5.4	224	13.9
	$P = 0.35$				$P < 0.001$			
No. of jobs held								
1	166	40.9	168	33.7	375	24.4	370	22.9
2	96	23.7	158	31.7	404	26.3	356	22.0
3	77	19.0	82	16.4	305	19.8	356	22.0
4	30	7.4	49	9.8	194	12.6	226	14.0
≥5	37	9.1	42	8.4	259	16.9	309	19.1
	$P = 0.03$				$P = 0.02$			

Table continues

carcinogenic risks by the International Agency for Research on Cancer (IARC) (16, 17). These lists are periodically updated and have been extensively used worldwide as a standardized tool to quantify the burden of occupational lung cancer (15, 18–21). While previous epidemiologic studies have helped to uncover the harmful effects of the list A occupations, there are still substantial uncertainties in relation to the list B occupations. More importantly, there remains a need to continue to evaluate occupations and try to uncover additional jobs and occupations that may contribute to the lung cancer burden.

The Environment And Genetics in Lung cancer Etiology (EAGLE) study provides this opportunity. It is one of the largest population-based case-control studies on lung cancer worldwide, designed to explore various characteristics (environmental and genetic) of lung cancer etiology as well as of smoking behavior (initiation, dependency, persistence) using an integrative approach that combines epidemiologic, clinical, and molecular data in a clearly defined population setting (22, 23).

MATERIALS AND METHODS

Study design

The study protocol (23) and first results on genetic, familial, and dietary factors and on previous chronic lung diseases have been published (24–30). Briefly, the study included 2,100 incident lung cancer cases and 2,120 population controls enrolled in April 2002–June 2005 in 216 municipalities including 5 cities (Milan, Monza, Brescia, Pavia, and Varese) in Lombardy, northern Italy. Subjects were 35–79 years of age at diagnosis (cases) or at sampling/enrollment (controls). Response rates (participants/eligible subjects) were 86.6% for cases and 72.4% for controls. Cases were admitted to 13 hospitals that examine more than 80% of lung cancer cases from the area and had any stage of primary cancer of the trachea, bronchus, and lung as well as morphology that were verified with tissue pathology (67.0%), cytology (28.0%), or review of clinical records (5.0%). Controls were randomly sampled from

Table 1. Continued

	Women				Men			
	Cases		Controls		Cases		Controls	
	No.	%	No.	%	No.	%	No.	%
Cigarette smoking								
Never	103	25.4	282	56.5	29	1.9	397	24.6
Former (quit >6 months ago)	116	28.6	110	22.0	723	47.0	799	49.4
Current	187	46.1	107	21.4	785	51.1	420	26.0
Unknown	0	0.0	0	0.0	0	0.0	1	0.1
	$P < 0.001$				$P < 0.001$			
Cigarette pack-years (mean (SD))	24.3 (23.1)		7.2 (13.5)		50.9 (28.7)		22.1 (23.2)	
	$P < 0.001$				$P < 0.001$			
Other cancer(s)[c]								
No	336	82.8	448	89.8	1,306	85.0	1,473	91.1
Yes	70	17.2	51	10.2	231	15.0	144	8.9
	$P = 0.002$				$P < 0.001$			
Lung cancer morphology								
Adenocarcinoma	220	54.2			582	37.9		
Squamous cell carcinoma	45	11.1			459	29.9		
Large cell carcinoma	28	6.9			61	4.0		
Non-small-cell carcinoma NOS	34	8.4			142	9.2		
Small cell carcinoma	38	9.4			157	10.2		
Other	26	6.4			65	4.2		
Not available	15	3.7			71	4.6		
			$P < 0.001$					

Abbreviations: EAGLE, Environment And Genetics in Lung cancer Etiology; NOS, not otherwise specified; SD, standard deviation.

[a] *P* values were derived from the chi-square test (categorical variables) or Student's *t* test (continuous variables).

[b] Percentages may not add to 100.0 because of rounding.

[c] Primary cancer(s) (previously or newly diagnosed) other than lung cancer.

population databases, frequency matched to case by residence (5 areas), gender, and age (5-year categories), and were contacted through family physicians. The study was approved by institutional review boards, and participants signed an informed consent.

Data collection

Extensive clinical data were collected for lung cancer cases, including morphology coded according to the *International Classification of Diseases for Oncology*, Third Edition (31) and categorized into major histologic subtypes based on World Health Organization/International Association for the Study of Lung Cancer classification (32). All subjects underwent a computer-assisted personal interview and blood sampling (or buccal rinse collection for a small percentage of study subjects), and they completed a self-administered questionnaire (both questionnaires are available in Italian and English on the EAGLE website (22)); lung tissue samples from cases were collected when available.

The interview included lifetime history (years of start/stop, industry, job title) of jobs held for at least 6 months. Industries and job titles were coded blindly with respect to case or control status by 2 of the authors (S. D. M., D. C.), both occupational physicians with training and experience in epidemiology and industrial hygiene, following the *International Standard Industrial Classification of All Economic Activities* (33) and the *International Standard Classification of Occupations* (34). Codes were then translated into occupations known (list A) or suspected (list B) to entail a carcinogenic risk to the lung (20, 21). The list B occupation filling station attendant, for which there are no specific codes, was identified through text search. Subjects with job titles from both lists were assigned to list A and to list B only if they had never worked in list A occupations; the reference group included subjects never employed in occupations on either list.

Statistical analysis

We calculated odds ratios and 95% confidence intervals using unconditional logistic regression, separately by gender; when evaluating risk for the main histologic subtypes (adenocarcinoma, squamous, and small cell carcinoma), we used polytomous (multinomial) logistic regression (35). To adjust for smoking, we evaluated different models (36–38) and finally chose the one with the lowest Akaike Information Criterion (39). The final model included the matching covariates area (5 categories) and age (5-year categories); cigarette smoking (ever/never); pack-years (continuous, mean centered: linear, quadratic, and cubic terms); time since quitting (0 for never/current smokers; 0.5, 1, 2, 5, 10, 20, ≥30 years); smoking (ever/never) of pipe, cigars, cigarillos; and number of jobs held (1, 2, 3, 4, ≥5). We performed an analysis by length of employment in list A occupations, calculated by summing working periods spent in list A jobs.

The population attributable fraction (PAF) for list A occupations was estimated by using the formula $P_{EC} \times (\text{OR} - 1)/\text{OR}$, where OR is the adjusted odds ratio and P_{EC} the proportion of cases exposed to at least one of the occupations (40, 41). To calculate the annual number of lung cancer cases attributable to list A occupations in Lombardy, we used the 2005 cancer incidence data (42).

We repeated selected analyses by including educational level as a surrogate of socioeconomic status (4 categories—none, elementary, middle, high school/higher degree combined—because no subject with a university degree had worked in list A occupations) (43, 44). Unless specified, the odds ratios given in this paper were not adjusted for education.

For subjects never employed in list A or list B occupations, we performed systematic exploratory analyses on single *International Standard Industrial Classification of All Economic Activities* codes (1–4 digits) and *International Standard Classification of Occupations* codes (1–3 and 5 digits). Results for industries/occupations for which at least 5 cases and 5 controls among men or women were exposed, and the odds ratio (education adjusted or not) was either doubled/halved or had a P value of ≤0.05, are given in Web Tables 1 and 2 (both are referred to as "Web table" in the text and are posted on the *Journal*'s website (http://aje.oupjournals.org/)).

Statistical analyses were performed by using Stata 10 software (45). Confidence limits of PAFs were calculated by using the command aflogit, which implemented the formulas proposed by Greenland and Drescher (46). All P values were 2-sided. We compared our estimates of odds ratio and PAF for list A occupations with those emerging from Italian and international case-control studies (18).

RESULTS

Subject characteristics

Of the 2,100 cases and 2,120 controls enrolled in the study, 1,943 (92.5%) and 2,116 (99.8%) were interviewed, respectively (Table 1; slight differences with respect to previous papers are due to data editing). Two-thirds of subjects were from the Milan area. Controls had a higher educational level (men) and had held more jobs. Among cases, one-fourth of women were never smokers versus only 2% of men. Almost half of the men (cases or controls) were former smokers compared with less than 30% of the women. In both genders, about 50% of cases and less than 30% of controls were current smokers. Men had smoked greater numbers of cigarettes. About 15%–17% of cases and 9%–10% of controls had primary cancer(s), previously or newly diagnosed, other than lung cancer. The majority of lung cancers were adenocarcinomas (>50% in women).

Occupations included in lists A and B

Among men, 177 cases (11.5%) and 100 controls (6.2%) had ever worked in list A occupations, with an overall odds ratio of 1.74 (Table 2); the corresponding PAF was 4.9% (95% confidence interval (CI): 2.0, 7.8). After further adjustment for dietary habits (consumption of red and processed meat, fruit and vegetables, and alcohol) and passive smoking (at home or the workplace), the odds ratio was practically unchanged (OR = 1.80). Most of the occupations in list A showed moderate to strong positive associations, notably (in terms of the OR and number of exposed subjects) the ceramic and refractory brick sector and occupations within the nonferrous basic industry. The risk excess for painters was modest (construction) or moderate (automobile and others). After adjustment for education, the general pattern of increased risks for list A was confirmed, although odds ratios were lower (Table 2, last 2 columns); on the basis of the overall excess of 53%, we estimated a PAF of 4.0% (95% CI: 0.8, 7.1).

When evaluating the risk excess for list A occupations by morphology (results not shown in tables), we found a stronger association for small-cell (OR = 2.04) and squamous (OR = 1.97) carcinomas compared with adenocarcinoma (OR = 1.38); however, the difference was not statistically significant ($P = 0.18$). Analysis by length of employment in list A occupations yielded the following results (not shown in tables): <10 years: OR = 1.64 (95% CI: 1.05, 2.56); 10–19 years: OR = 3.89 (95% CI: 1.80, 8.40); 20–29 years: OR = 1.30 (95% CI: 0.57, 3.00); ≥30 years: OR = 1.79 (95% CI: 0.94, 3.40) (P for trend = 0.001).

In total, 345 cases (22.4%) and 346 controls (21.4%) among men had been working in occupations in list B, with no overall increased risk (Table 3). We found a marked elevated risk for filling station attendants. The excess for bus or truck drivers was modest but was based on a large number of subjects; moderate to strong associations (based on a few subjects) were observed for several other occupations, including leather tanners and processors, glass workers, and welders. The odds ratios were reduced after adjustment for education (Table 3, last 2 columns).

Among women, only 3 cases (1 in ceramic and pottery, 2 in nonferrous industries) and 2 controls (painters) had ever been employed in list A occupations, with an odds ratio of 4.05 and a PAF of 0.6% (95% CI: −2.7, 3.7). For list B occupations, the odds ratio was 0.94 (95% CI: 0.46, 1.94) based on 24 cases and 26 controls exposed; there were few exposed women in specific occupations, with the exception of laundry and dry cleaners (12 cases and 11 controls exposed), for which we calculated an odds ratio of 1.26 (95% CI: 0.46, 3.41).

Our odds ratio estimate for list A occupations was very close to the average of 1.7 emerging from Italian studies.

Table 2. Lung Cancer Risk for Industries/Occupations Known (List A) to Be Associated With Lung Cancer for Men in the EAGLE Study, Lombardy, Italy, 2002–2005[a]

Industry (ISIC Code)	Occupation/Process (ISCO Code)[b]	No. of Cases	No. of Controls	OR[c]	95% CI	OR_E[d]	95% CI
Never worked in list A/B industries/occupations (reference)[e]		1,015	1,171	1.00		1.00	
Ever worked in list A industries/occupations		177	100	1.74	1.27, 2.38	1.53	1.10, 2.11
Agriculture (1110)	Vineyard workers using arsenical insecticides (before 1970) (62330)	4	3				
Mining and quarrying		9	7	1.63	0.46, 5.78	1.41	0.40, 4.96
Mining and quarrying, various (2301, 2302, 2902, 2909)	Arsenic, uranium, iron-ore, asbestos mining, talc mining/milling (03810/90, 70020, 711* (not 71140), 71230–60, 71290, 97345)	5	5	1.04	0.24, 4.39	0.93	0.22, 3.89
Granite mining (2901)	Granite mining (71110/30/90, 71220/30/40/90)	5	2	7.09	0.59, 85.43	5.96	0.50, 70.64
Ceramic and refractory brick (3610, 3691) or (Any ISIC)	Ceramic and pottery workers (Blue collar) or (892*, 89350/60/90, 89930/40/50/6090)	26	11	2.64	1.13, 6.19	2.29	0.97, 5.39
Granite production (3699)	Cutting, polishing, etc., of granites stones (82020/30/40/50/90)	7	6	1.17	0.33, 4.12	1.02	0.29, 3.60
Asbestos production (3699) or (Any ISIC)	Insulated material production (74190, 751*, 752*, 75415/20/25/70/75/90, 755*, 75670) or (94330)	2	0				
Metals (iron and steel, basic) (3710)	Iron and steel founding (724*, 725*)	4	4				
Metals (nonferrous, basic; smelting, alloying, refining, etc.)		45	22	2.45	1.31, 4.60	2.20	1.17, 4.14
(3720) or (Any ISIC)	Copper, zinc, cadmium, aluminum, nickel, chromates, beryllium (Blue collar workers) or (72440/50/90)	12	9	1.21	0.43, 3.44	1.04	0.36, 2.97
(Any ISIC)	Pickling operations (72940)	17	6	3.66	1.21, 11.04	3.22	1.06, 9.72
(Any ISIC)	Chromium plating (728*, 72940)	31	11	3.58	1.57, 8.17	3.23	1.41, 7.36
(Any ISIC)	Electroplating (72820/90, 72940)	28	11	3.22	1.38, 7.46	2.93	1.26, 6.79
(Any ISIC)	Brazing (87245)	3	2				
Shipbuilding/railroad equipment (3841, 3842) or (Any ISIC)	Shipyard/dockyard, railroad manufacture workers (Blue collar) or (84125/30, 87130)	9	3	3.83	0.75, 19.54	3.36	0.66, 17.10
Gas (3540, 4102) or (Any ISIC)	Coke plant and gas production workers (74* (not 745*)) or (7492*)	0	0				
Construction		8	7	1.74	0.48, 6.23	1.45	0.40, 5.19
(Any ISIC)	Insulators and pipe coverers (956*)	2	1				
(Any ISIC)	Roofers (95320/30/40/90)	2	2				
(Any ISIC)	Asphalt workers (95340, 97450/60)	5	5	1.72	0.36, 8.12	1.42	0.30, 6.75
Other		76	44	1.27	0.81, 1.98	1.09	0.69, 1.73
(Any ISIC)	Painters (construction) (931*)	49	30	1.13	0.66, 1.94	0.98	0.56, 1.69
(Any ISIC)	Painters (automobile, others) (939*)	28	16	1.40	0.69, 2.88	1.21	0.59, 2.51

Abbreviations: CI, confidence interval; EAGLE, Environment And Genetics in Lung cancer Etiology; ISCO, *International Standard Classification of Occupations*; ISIC, *International Standard Industrial Classification of All Economic Activities*; OR, odds ratio.

[a] Calculations were performed for occupations with at least 5 exposed cases.

[b] An asterisk indicates that all 5-digit codes within that code are considered.

[c] Calculated with logistic regression models, adjusted for area of residence, age, smoking, and number of jobs held.

[d] Also adjusted for education.

[e] Occupations known (list A) or suspected (list B) to be associated with lung cancer; refer to Ahrens and Merletti (20) and Mirabelli et al. (21) for exact definitions and codes.

Table 3. Lung Cancer Risk for Industries/Occupations Suspected (List B) to Be Associated With Lung Cancer for Men in the EAGLE Study, Lombardy, Italy, 2002–2005[a]

Industry (ISIC Code)	Occupation/Process (ISCO Code)[b]	No. of Cases	No. of Controls	OR[c]	95% CI	OR_E[d]	95% CI
Never worked in list A/B industries/occupations (reference)[e]		1,015	1,171	1.00		1.00	
Ever worked in list B (never in list A) industries/occupations		345	346	1.06	0.86, 1.31	0.94	0.75, 1.17
Food (3111) or (Any ISIC)	Butchers and meat workers (Blue collar, 45130) or (773*)	24	26	0.77	0.39, 1.53	0.70	0.35, 1.38
Leather (3231) or (Any ISIC)	Tanners and processors (Blue collar) or (761*)	8	4	2.73	0.56, 13.22	2.51	0.52, 12.04
Wood and wood products (Any ISIC)	Carpenters, joiners (81*, 954*)	76	66	1.13	0.74, 1.72	0.99	0.64, 1.52
Printing (3420)	Rotogravure/machine-rooms workers, printing pressmen, binders, others (92110, 922*, 92630/50)	38	48	0.85	0.50, 1.44	0.79	0.47, 1.35
Rubber (3551, 3559) or (Any ISIC)	Various occupations in rubber manufacture (Blue collar) or (90120–40, 90190, 902*)	19	26	0.72	0.35, 1.48	0.65	0.31, 1.34
Glass (3620) or (Any ISIC)	Glass workers (art glass, container and pressed ware) (Blue collar) or (891*, 89320/30/40, 89440, 89920/70/90)	17	9	1.54	0.57, 4.15	1.33	0.49, 3.56
Motor vehicle manufacturing and repair		43	51	1.22	0.73, 2.03	1.08	0.65, 1.81
(3843, 9513)	Machine-tool operators (831*, 83220/30, 833*, 834*; 83960)	9	12	0.68	0.25, 1.88	0.61	0.22, 1.72
(3843, 9513) or (3843)	Mechanics (843*) or (84985)	31	40	1.29	0.72, 2.33	1.14	0.63, 2.07
(3843, 9513)	Welders and flame cutters (872* (not 87245))	4	1				
Transport		157	141	1.20	0.89, 1.63	1.04	0.76, 1.43
(Any ISIC)	Railroad workers (983*, 98440)	8	8	0.73	0.21, 2.60	0.67	0.19, 2.37
(Any ISIC)	Bus and truck drivers (98540–60)	149	129	1.23	0.90, 1.68	1.07	0.77, 1.48
(Any ISIC)	Operators of excavating machines (97420–45, 97455, 97470, 97490)	8	7	1.17	0.27, 5.05	0.96	0.22, 4.16
Trade	Filling station attendants (identified through text search)	16	4	7.41	1.76, 31.17	6.64	1.58, 27.94
Other (Any ISIC)	Launderers, dry cleaners, and pressers (560*)	2	3				

Abbreviations: CI, confidence interval; EAGLE, Environment And Genetics in Lung cancer Etiology; ISCO, *International Standard Classification of Occupations*; ISIC, *International Standard Industrial Classification of All Economic Activities*; OR, odds ratio.

[a] Calculations were performed for occupations with at least 5 exposed cases.

[b] An asterisk indicates that all 5-digit codes within that code are considered.

[c] Calculated with logistic regression models, adjusted for area of residence, age, smoking, and number of jobs held.

[d] Also adjusted for education.

[e] Occupations known (list A) or suspected (list B) to be associated with lung cancer; refer to Ahrens and Merletti (20) and Mirabelli et al. (21) for exact definitions and codes.

However, we found a lower PAF because of the lower proportion of exposed cases (Table 4).

Other industries and occupations not included in lists A and B

For both genders, we found elevated risks for several industry branches within the categories manufacture of fabricated metal products, machinery and equipment; other manufacturing industries; and barber and beauty shops (Web Table 1). From the analysis of occupations (Web Table 2), we found elevated risks for both genders for professional and technical workers not elsewhere classified, hairdressers and related workers, and several occupations within major group 7/8/9 (production and related workers, transport equipment operators and

Table 4. Population Attributable Fraction for Industries/Occupations Known (List A) to Be Associated With Lung Cancer in Italian General-Population Case-Control Studies[a]

Study (Reference No.)	Type of Controls	Study Place (Area of Italy)	Study Period	No. of Cases: Exposed/Total	P_{EC}, %	OR[b]	95% CI	PAF, %
Ronco et al., 1988 (69)	Population	Settimo Torinese (Northwest)	1976–1980	12/58	20.7	2.3	0.9, 5.9	11.9
	Population	Rivoli (Northwest)	1976–1980	11/68	16.2	1.4	0.6, 3.4	4.9
Bovenzi et al., 1993 (66)	Population	Trieste (Northeast)	1979–1981; 1985–1986	218/756	28.8	2.2	1.7, 3.0	16.0
Simonato et al., 2000 (70)	Population	Venice Islands (Northeast)	1992–1994	18/73	24.7	1.0	0.3, 3.0	0.0
	Population	Venice Inland (Northeast)	1992–1994	28/146	19.2	1.3	0.6, 2.2	4.4
Richiardi et al., 2004 (52)	Population	Turin (Northwest)	1990–1991	114/482	23.7	1.9	1.3, 2.7	11.1
	Population	Eastern Veneto (Northeast)	1991–1992	60/474	12.7	2.5	1.5, 4.2	7.8
Fano et al., 2004 (67)	Population	Civitavecchia (Center)	1987–1995	26/234	11.1	1.3	0.8, 2.2	2.6
Mean					19.6	1.7		7.3
EAGLE (this study)	Population	Lombardy (North)	2002–2005	177/1,537	11.5	1.74	1.27, 2.38	4.9

Abbreviations: CI, confidence interval; EAGLE, Environment And Genetics in Lung cancer Etiology; OR, odds ratio; PAF, population attributable fraction; P_{EC}, proportion of exposed cases.
[a] All results are for men except for Fano et al. (67), which included 201 (85.9%) men and 33 (14.1%) women.
[b] Adjusted for smoking.

laborers). For men, odds ratios were elevated for motor vehicle drivers.

DISCUSSION

In this large, population-based case-control study performed in 2002–2005 in Lombardy, northern Italy—the most populated (about 9,750,000 inhabitants), economically relevant, and industrialized region in Italy—we found a relative risk excess of 74% for men ever employed in occupations known (list A) to be associated with lung cancer, with the largest contributions from the ceramic and refractory brick and the nonferrous basic industries. The PAF was 4.9%. For women, the relative risk excess was greater (OR = 4.05), although imprecise because of the very low numbers of women exposed. Of the occupations suspected (list B) to be associated with lung cancer, we found a marked excess for filling station attendants (men) and suggestive increases for bus and truck drivers (men) and launderers and dry cleaners (women).

This study confirmed the important role of past occupational exposures as a determinant of lung cancer risk at the beginning of the new century. Applying the PAF of 4.9% to the 4,515 incident male cases of lung cancer that occurred in 2005 in Lombardy (42), we estimated that 221 cases per year (95% CI: 90, 352), or 181 (95% CI: 36, 321) for the education-adjusted PAF, were attributable to past employment in list A occupations. These figures contrast with the low number of occupational lung cancers officially reported to and compensated by the National Insurance Institute for Work Injuries (Istituto Nazionale per l'Assicurazione contro gli Infortuni sul Lavoro, INAIL); for instance, in 1999–2004, only 399 work-related lung cancer cases (on average, 66.5/year) were reported in Lombardy, and about half of them were compensated (47). The low PAF for list A occupations among women was expected, given that exposure to most occupational lung carcinogens occurred in workplaces in which women constituted a minority (48).

The major strengths of the present study are the enrollment of incident cases and randomly sampled population controls; the large sample size; the unusually high participation rates, especially considering that biologic samples were requested; and the face-to-face collection of detailed information with a structured questionnaire by trained interviewers. Still, in interpreting the results, we considered several possible sources of bias. Reliability of self-reported job history is usually considered good (12, 15) and not a source of important recall bias. Blind coding of occupations eliminated the possibility of differential bias, although a certain degree of nondifferential misclassification is practically unavoidable, leading to an average bias toward the null (11, 49, 50). We exploited the detailed interview data to adjust for different smoking-related characteristics.

Adjustment for education (an indicator of socioeconomic status) is usually performed to control for unmeasured nonoccupational (e.g., lifestyle) confounders or to address differential selection (nonresponse) between cases and controls (44, 51), although some authors argue that doing so would lead to underestimated occupational risks (43). Our results were not altered (OR = 1.80) by adjustment for diet, alcohol consumption, and passive smoking. Moreover, to evaluate potential differential participation, we compared educational level among cases and controls who refused to participate in the study but consented to respond to a few selected questions: contrary to observations by others (51, 52), we found no association ($P = 0.68$). For these reasons, the odds ratios not adjusted for education are probably a better estimate of the effect of occupation in our study, but we presented both types of estimates here (43, 44).

Our relative risk excess for list A occupations among men is consistent with those found in different countries since the 1970s (18, 53–64). When we excluded a study conducted in a mining area with an unusually large excess (57), the average odds ratio was 1.4 (range, 0.4–1.9). The odds ratio for list A occupations (men) also closely corresponds with the findings from Italian studies (18, 52, 65–70) (Table 4). However, we found a lower PAF, for several reasons. First, those studies were conducted in areas with a high concentration of workers exposed to asbestos in shipbuilding and railroad equipment manufacturing (52, 66) or to multiple carcinogens in foundries and the chemical and metal industries (69, 70). Second, we found lower risks for painters, the occupation with the highest number of exposed cases (Table 2); as a result, the overall excess was lower (OR = 2.23 for list A occupations other than painters). Third, occupational exposure to carcinogens has been decreasing over time because of improved workplace conditions.

The lack of an overall association for list B occupations is in agreement with a recent case-control study conducted in northern Italy (52). The findings for individual occupations in list B are only suggestive because the excess risk was moderate or the number of exposed subjects was small. The only clear excess was for filling station attendants (men), for which the evidence in the literature is conflicting (71–73). The 23% increased risk for bus and truck drivers deserves mention because it was based on a substantial number of exposed workers and because we found an excess for other motor vehicle drivers not included among list B occupations. For women, we found a moderate risk increase for launderers and dry cleaners, a finding reported in other studies (52, 60, 74–77).

The results for single *International Standard Industrial Classification of All Economic Activities* and *International Standard Classification of Occupations* codes not included in list A or B should be regarded as suggestive because of poor sensitivity and specificity in defining exposures (15, 19) and multiple comparison issues (78). Some of the increased risks deserve mention because they are biologically plausible, were consistent across gender, or were already reported in the literature, in particular metal production and processing (15, 19, 52, 59, 79–89), barbers and hairdressers (15, 16, 19, 82, 90–95), and motor vehicle drivers (men) (90, 96–103).

In conclusion, the findings of this study confirm the need for continuous monitoring and improved control of work-related exposures, both for prevention and workers' compensation purposes. Future occupational health studies should improve their ability to address interindividual variability in response to the lower exposures in work settings.

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Author affiliations: Unit of Epidemiology, Department of Preventive Medicine, Fondazione IRCCS Ospedale Maggiore Policlinico, Mangiagalli e Regina Elena, Milan, Italy (Dario Consonni, Sara De Matteis, Angela Cecilia Pesatori, Pier Alberto Bertazzi); EPOCA Research Center, Department of Occupational and Environmental Health, Università degli Studi di Milano, Milan, Italy (Dario Consonni, Sara De Matteis, Angela Cecilia Pesatori, Pier Alberto Bertazzi); and Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, Maryland (Jay H. Lubin, Sholom Wacholder, Margaret Tucker, Neil E. Caporaso, Maria Teresa Landi).

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