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Impact of occupational carcinogens on lung cancer risk in a general population

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Background Exposure to occupational carcinogens is an important preventable cause of lung cancer. Most of the previous studies were in highly exposed industrial cohorts. Our aim was to quantify lung cancer burden attributable to occupational carcinogens in a general population.

Methods We applied a new job–exposure matrix (JEM) to translate lifetime work histories, collected by personal interview and coded into standard job titles, into never, low and high exposure levels for six known/suspected occupational lung carcinogens in the Environment and Genetics in Lung cancer Etiology (EAGLE) population-based case–control study, conducted in Lombardy region, Italy, in 2002–05. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated in men (1537 cases and 1617 controls), by logistic regression adjusted for potential confounders, including smoking and co-exposure to JEM carcinogens. The population attributable fraction (PAF) was estimated as impact measure.

Results Men showed an increased lung cancer risk even at low exposure to asbestos (OR: 1.76; 95% CI: 1.42–2.18), crystalline silica (OR: 1.31; 95% CI: 1.00–1.71) and nickel–chromium (OR: 1.18; 95% CI: 0.90–1.53); risk increased with exposure level. For polycyclic aromatic hydrocarbons, an increased risk (OR: 1.64; 95% CI: 0.99–2.70) was found only for high exposures. The PAFs for any exposure to asbestos, silica and nickel–chromium were 18.1, 5.7 and 7.0%, respectively, equivalent to an overall PAF of 22.5% (95% CI: 14.1–30.0). This corresponds to about 1016 (95% CI: 637–1355) male lung cancer cases/year in Lombardy.

Conclusions These findings support the substantial role of selected occupational carcinogens on lung cancer burden, even at low exposures, in a general population.

Keywords lung neoplasms, case–control study, carcinogens, occupational health

Introduction

Lung cancer is the leading tumour for mortality worldwide.[1] Exposure to occupational carcinogens is an important preventable cause of lung cancer.[2] A review, mainly based on industrial cohorts, estimated that in 2000 about 88 000 (10%, men) and 14 000 (5%, women) lung cancer deaths worldwide were attributable to eight known or suspected occupational carcinogens (arsenic, asbestos, beryllium, cadmium, chromium, diesel fumes, nickel and silica).[2]

Although industrial cohorts are useful for investigating particular exposures at high levels, they are not suitable to estimate their impact at a population level.[3] Population-based case–control studies remain the most efficient epidemiological design to assess the impact of multiple occupational exposures among the broad range of industries and jobs occurring in a community.[4]

The Environment and Genetics in Lung cancer Etiology (EAGLE) study is a large population-based case–control study performed in the Lombardy region, Italy, in 2002–05, designed to evaluate genetic and environmental lung cancer determinants, including occupational exposures, in an integrated approach.[5] An earlier EAGLE report[6] found a 1.74-fold increased lung cancer risk among males ever employed in occupations 'known to entail an increased risk for lung cancer', with a corresponding population attributable fraction (PAF) of 4.9%.

In the present work, we went beyond those findings to evaluate, across all occupations, the impact of six selected known or suspected occupational lung carcinogens on lung cancer risk. We applied a new general population job–exposure matrix (JEM), recently used in an international project of pooled case–control studies.[7,8] This method converts each job title into the exposure levels entailed by it, gathering workers with common exposure across job categories.[9] The large study size allowed evaluation of risk by lung cancer histology and the interaction between carcinogens and cigarette smoking.

Materials and Methods

Study design

The EAGLE study, described in detail previously,[5] includes 2100 incident lung cancer cases and 2120 population controls enrolled in April 2002 to June 2005 in 216 municipalities, including the cities of Milan, Monza, Brescia, Pavia and Varese, in Lombardy, the most populated (over nine million inhabitants) and industrialized region of Italy. Subjects were 35–79 years of age at diagnosis (cases) or at sampling/enrolment (controls). Response rates (participants/eligible subjects) were 86.6% (cases) and 72.4% (controls).

Cases were newly diagnosed primary lung cancers, mostly (95%) histopathologically verified. They were recruited in 13 hospitals that cover over 80% of the lung cancer cases from the study area. Controls were randomly sampled from population databases, frequency matched to cases by residence (five areas), gender and age (5-year categories) and contacted through family physicians. The study was approved by institutional review boards and all participants signed an informed consent form.

Data collection

All subjects underwent a computer-assisted personal interview, including detailed lifetime history of smoking and jobs held for at least 6 months (industry branch, job title, years of start and stop). Industry and job title were then coded blindly with respect to case–control status by two of the authors (S.D.M., D.C.), by using the International Standard Industrial Classification of All Economic Activities (ISIC), 1971[10] and the International Standard Classification for Occupations (ISCO), 1968.[11]

Exposure assessment

We applied the 'DOM-JEM', recently developed by three of the authors (H.K., R.V. and S.P.) within the SYNERGY project, an international pooled analysis of lung cancer case–control studies coordinated by the International Agency for Research on Cancer (IARC), the Institute for Prevention and Occupational Medicine of the German Social Accident Insurance, Institute of the Ruhr-University Bochum (IPA) and the Institute for Risk Assessment Sciences at Utrecht University (IRAS) (http://synergy.iarc.fr). This JEM was created a priori (i.e. independently from any study population) to be applied in community-based studies. Experts' rating was based on intensity and probability of exposure.[7] The JEM translates all job titles (five-digit ISCO codes) into exposure to selected agents, ranked as 0, 1 and 2 for no, low and high exposure, respectively. The six known or suspected occupational lung carcinogens included in the 'DOM-JEM' were asbestos, crystalline silica, polycyclic aromatic hydrocarbons (PAH), diesel motor exhausts (DME), chromium compounds (Cr) and nickel compounds (Ni). These agents had been previously selected for the SYNERGY project, according to the following criteria: (i) IARC evaluation: known (Group 1) or suspected (Group 2A/2B) lung carcinogens; (ii) relevance for recognition of occupational diseases associated with these agents (recognized number of cases per year by Workers Health Insurance); (iii) prevalence of exposure and probability of simultaneous exposures to two or more agents over the course of an individual job history in the general population; and (iv) available information for quantitative exposure assessment.

We merged the five-digit ISCO codes for jobs held by each subject with the JEM to estimate the individual exposures.

Statistical analysis

For each carcinogen, we evaluated a dichotomous exposure indicator (never/any) and an ordinal variable for intensity of exposure (never/low/high). Further, we analysed duration and cumulative exposure as the sum of the job-specific (intensity score × duration) products (with scores set to 1 and 4 for low and high exposure, respectively). Latency was defined as time at lung cancer diagnosis or study enrolment since first exposure. The analyses were conducted using both categorical and continuous variables. For duration and cumulative exposure, we defined the categories according to the quartiles of the exposure distribution among controls for each carcinogen. For latency, we used predefined categories of exposure (never, 20–29, 30–39, 40–49, 50–59 and ⩾60 years) to explore their impact on a broader range of years since first exposure. When analysing those variables as continuous, we used the ln $(1+x)$ transformation to normalize their distribution. We evaluated co-exposure to the JEM carcinogens using Spearman's rank correlation coefficient (ρ_s).

For each carcinogen exposure, we calculated odds ratios (ORs), 95% confidence intervals (95% CIs) and tests for trend, using unconditional logistic regression, separately for males and females, taking subjects never exposed to the carcinogen as reference. All regression models included the following covariates: residential area (five categories); age (5-year categories); cigarette smoking (ever/never); pack-years (continuous, mean-centred: 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 other types of tobacco (pipe, cigars and cigarillos) and, for each agent, co-exposure to the other carcinogens included in the JEM. We also adjusted for number of jobs held (1, 2, 3, 4, ⩾5), since this variable was negatively associated with lung cancer among non-exposed subjects ($P_{trend}=0.014$) and positively associated with exposure to carcinogens among controls ($P<0.0001$ from chi-squared test). We used the same approach in our previous article on occupations known/suspected to be associated with lung cancer risk.[6] A similar approach was also used in other case–control studies from Northern Italy and France.[12,13]

We repeated selected analyses after adjusting for education (none, elementary, middle and high school/higher degree) as a surrogate of socioeconomic status.

For the exposures showing an increased OR, we calculated the carcinogen specific and overall PAF by using the formula $P_{EC} \times (OR - 1)/OR$,[14] where OR is the adjusted OR and P_{EC} is the proportion of cases ever exposed to the carcinogen under study. The definition of exposure we used when calculating PAF estimates considers subjects unexposed to the carcinogen under study as belonging to the 'reference' category and everyone even slightly exposed as belonging to the 'exposed' category. Estimates of PAF when using this broad definition of 'exposed' are less prone to bias from non-differential misclassification of exposure, the form of misclassification expected with a JEM approach.[15] We estimated ORs for the three main histological lung cancer types (adenocarcinoma, squamous cell and small-cell carcinomas) and tested their homogeneity in a multinomial logistic regression model.

We evaluated interactions between each carcinogen (never/any exposure) and cigarette smoking status (never/former/current) on the multiplicative scale, by comparing the likelihood of a logistic regression model containing the main effects of the carcinogen and smoking with that of a model also containing their interaction. As reference, we used subjects never exposed to both smoking and the specific carcinogen under study. In these models, we did not adjust for co-exposure to the other JEM carcinogens to avoid too few subjects per strata.

All *P*-values were two-sided. Analyses were performed with Stata 11.[16] Confidence limits of PAF were calculated with the command aflogit that implemented the formulas proposed by Greenland and Drescher.[17]

Results

Of the 2100 cases and 2120 controls enrolled in our study, 1943 (92.5%) and 2116 (99.8%) were interviewed, respectively (Table 1). Two-thirds of the subjects came from the Milan area. Among men, controls had higher education and held more jobs than cases. About 14–15% of the cases and 6–7% of the controls had previously or newly diagnosed primary cancer(s) other than lung cancer. Among cases, one-fourth of the women were never smokers vs only 2% of men. In both genders, current smokers were ~50% among cases and <30% among controls. Almost half of the men (cases or controls) were former (quit >6 months ago) smokers when compared with <30% among women. The majority of lung cancers were adenocarcinomas (>50% in women).

Lifetime co-exposure to pairs of JEM carcinogens was frequent (Supplementary Table 1, available as Supplementary data at *IJE* online). In particular, Cr and Ni were strongly correlated: among men $\rho_s=0.75$ in cases; $\rho_s=0.83$ in controls; among women $\rho_s=1.00$ in both; all with $P<0.001$. For this reason, we combined these agents in a single variable Ni–Cr.

Very few women were found to be exposed to the six occupational lung carcinogens, particularly at high levels, except asbestos (11.3% among cases and 10.0% among controls) and PAH (12.1% among cases and 9.8% among controls) (Supplementary Table 2, available as Supplementary data at *IJE* online). Although based on small numbers, we found an increased risk for any exposure to Ni–Cr (OR = 2.80; 95% CI: 1.20–6.54), with a positive trend for intensity ($P=0.03$).

Table 1 Selected characteristics of lung cancer cases and controls with interview data available: the EAGLE study, Lombardy, Italy, 2002–05[a,b]

Subjects characteristics	Women		Men	
	Cases *N* (%)	Controls *N* (%)	Cases *N* (%)	Controls *N* (%)
Total participants enrolled	448	500	1652	1620
Interviewed	406 (100.0)	499 (100.0)	1537 (100.0)	1617 (100.0)
Area of residence				
Milan	288 (70.9)	349 (69.9)	987 (64.2)	1089 (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-value	0.55		0.17	
Age (years)				
Mean (SD)	64.8 (10.1)	64.1 (10.1)	66.8 (7.9)	65.8 (8.1)
P-value	0.32		<0.001	
Education level				
None	21 (5.2)	24 (4.8)	91 (5.9)	66 (4.1)
Elementary	128 (31.5)	143 (28.7)	625 (40.7)	431 (26.7)
Middle	134 (33.0)	158 (31.7)	424 (27.6)	455 (28.1)
High	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-value	0.35		<0.001	
Number of jobs				
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-value	0.03		0.02	
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-value	<0.001		<0.001	
Cigarette pack-years				
Mean (SD)	24.3 (23.1)	7.2 (13.5)	50.9 (28.7)	22.1 (23.2)
P-value	<0.001		<0.001	
Other cancer(s)[c]				
No	336 (82.8)	448 (89.8)	1306 (85.0)	1473 (91.1)
Yes	70 (17.2)	51 (10.2)	231 (15.0)	144 (8.9)
P-value	0.002		0.001	
Lung cancer morphology				
Adenocarcinoma	220 (54.2)		582 (37.9)	

(continued)

Table 1 Continued

Subjects characteristics	Women		Men	
	Cases *N* (%)	Controls *N* (%)	Cases *N* (%)	Controls *N* (%)
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)	
Others	26 (6.4)		65 (4.2)	
Not available	15 (3.7)		71 (4.6)	
P-value		<0.001		

NOS, not otherwise specified; SD, standard deviation.
[a]*P*-values were derived from the χ^2 test (categorical variables) or Student's *t*-test (continuous variables) between cases and controls.
[b]Percentages may not add to 100.0 because of rounding.
[c]Primary cancer(s) (previously or newly diagnosed) other than lung cancer.

Since OR estimates were unstable, we restricted all subsequent analyses to men.

Men were most commonly exposed to asbestos (41.1% among cases and 32.2% among controls) and DME (38.8% among cases and 38.5% among controls). Intensity levels for the majority of exposed subjects were low (Table 2). In the regression model adjusted for area, age, cigarette smoking, other types of tobacco and number of jobs held, we found increased ORs for lung cancer for any and even low exposure to asbestos, silica and Ni–Cr, with positive trends for intensity of exposure. For PAH, only subjects with high exposure had increased risk. After adjusting also for co-exposure to the other JEM carcinogens, the estimates for associations tended to decrease for all carcinogens, in particular for high exposure to asbestos, low exposure to Ni–Cr and high exposure to PAH.

No association was found for DME. The PAFs for any exposure to asbestos, silica and Ni–Cr were 18.1%, 5.7% and 7.0%, respectively, corresponding to an overall PAF of 22.5% (95% CI: 14.1–30.0). Without adjusting for number of jobs or after further adjustment for education, the ORs did not change appreciably (data not shown). Exclusion of subjects who had other cancers or adjustment for an indicator for another cancer did not substantially alter the results (data not shown). We also used a cut-off of 2 years since quitting smoking to define the former smokers, but the results were unchanged (data not shown).

Asbestos showed positive, although not monotonic, exposure–response trends for duration, cumulative exposure and latency ($P < 0.0001$). Weaker trends, and not for all these variables, were found for silica and Ni–Cr exposure. Using duration, cumulative exposure and latency as continuous variables, these results were substantially confirmed (Supplementary Tables 3–5, available as Supplementary data at *IJE* online).

We found differences by histology for silica (any exposure) ($P_{\text{homogeneity}} = 0.027$), with an increased risk for squamous and small-cell carcinomas, but not for adenocarcinomas (Table 3). We obtained similar results for cumulative exposure ($P = 0.004$) (data not shown).

When considering joint exposures with smoking (Table 4), we found increased ORs for former and current smokers exposed to any level of asbestos, silica and Ni–Cr. For never smokers, the increased risk was clear only in those exposed to asbestos, probably due to the small number of never smokers exposed to the other carcinogens. We found no deviation from a multiplicative interaction model between these carcinogens and smoking ($0.19 < P_{\text{interaction}} < 0.94$ from 2-df log-likelihood ratio tests), confirming the independent effect of these factors on a multiplicative scale.

Discussion

Our findings provide robust evidence that in men past occupational exposure to asbestos, silica and Ni–Cr, even at low levels, contributes substantially to the current lung cancer burden with PAFs of 18.1%, 5.7% and 7.0%, respectively. Exposure to PAH showed increased risk only at high levels.

The 1.76-fold increased risk found for low occupational exposure to asbestos captures effects beyond the small numbers of highly exposed subjects employed in asbestos production, shipbuilding and railroad equipment, as in the majority of previous studies.[18–20]

One recent population-based study failed to detect a positive association at low exposures, probably due to small sample size,[21] and another found a null result probably because of the reported 'poor inter-team agreement' in defining asbestos exposure.[22] In our study, asbestos-exposed subjects worked mainly in the construction industry (e.g. plumbers and electricians). This sector is known to have, even today,

Table 2 Lung cancer risk for exposure to JEM carcinogens for men in the EAGLE study, Lombardy, Italy, 2002–05[a]

Carcinogens	Cases, *N* (%)	Controls, *N* (%)	OR[b] (95% CI)	OR[c] (95% CI)	PAF[d] % (95% CI)
Asbestos					
Never[e]	905 (58.9)	1097 (67.8)	1.00	1.00	
Any	632 (41.1)	520 (32.2)	1.73 (1.43–2.09)	1.78 (1.46–2.18)	18.1 (12.6–23.3)
Low	546 (35.5)	448 (27.7)	1.68 (1.38–2.04)	1.76 (1.42–2.18)	
High	86 (5.6)	72 (4.5)	2.09 (1.39–3.13)	1.51 (0.94– 2.44)	
P-value			0.001	<0.001	
Silica					
Never[e]	1166 (75.9)	1363 (84.3)	1.00	1.00	
Any	371 (24.1)	254 (15.7)	1.38 (1.10–1.72)	1.31 (1.02–1.68)	5.7 (0.4–10.6)
Low	328 (21.3)	226 (14.0)	1.37 (1.09–1.73)	1.31 (1.00–1.71)	
High	43 (2.8)	28 (1.7)	1.46 (0.81–2.61)	1.41 (0.77–2.55)	
P-value			0.006	0.02	
Ni–Cr					
Never[e]	1041 (67.7)	1216 (75.2)	1.00	1.00	
Any	496 (32.3)	401 (24.8)	1.41 (1.16–1.72)	1.28 (1.00–1.63)	7.0 (0.2–13.3)
Low	370 (24.1)	328 (20.3)	1.33 (1.08–1.65)	1.18 (0.90–1.53)	
High	126 (8.2)	73 (4.5)	1.77 (1.22–2.56)	1.31 (0.86–1.97)	
P-value			<0.001	0.06	
PAH					
Never[e]	1137 (74.0)	1235 (76.4)	1.00	1.00	
Any	400 (26.0)	382 (23.6)	1.11 (0.90–1.36)	0.87 (0.68–1.10)	
Low	284 (18.5)	321 (19.9)	0.90 (0.72–1.13)	0.78 (0.61–1.00)	
High	116 (7.5)	61 (3.7)	2.46 (1.65–3.67)	1.64 (0.99–2.70)	
P-value			0.007	0.75	
DME					
Never[e]	940 (61.2)	994 (61.5)	1.00	1.00	
Any	597 (38.8)	623 (38.5)	0.90 (0.75–1.09)	0.82 (0.67–1.00)	
Low	476 (31.0)	500 (30.9)	0.89 (0.73–1.09)	0.85 (0.69–1.05)	
High	121 (7.8)	123 (7.6)	0.96 (0.68–1.35)	0.70 (0.48–1.00)	
P-value			0.44	0.047	

DME, diesel motor exhausts; Ni–Cr, nickel and chromium compounds; PAF, population attributable fraction;.
[a]*P*-values were calculated from test for linear trend for never/low/high exposure.
[b]OR calculated with unconditional logistic regression models, adjusted for area, age, smoking and number of jobs.
[c]OR adjusted as specified in the above footnote and also for co-exposure to the other JEM carcinogens.
[d]PAF calculated for any exposure to each carcinogen associated with an increased risk using, as specified in the above footnote, OR and percentage of cases exposed to each carcinogen.
[e]Reference category: never exposed to the specific carcinogen.

a high prevalence of exposure to asbestos: the Occupational Safety & Health Administration (OSHA) recently estimated 1.3 million workers still being exposed in the USA in the construction and general industry.[23] In Italy, it was reported that about 70 000 construction workers in the period 2000–03 were still exposed to asbestos.[24]

We found a 1.31-fold increased risk for exposure to crystalline silica even among a majority of low-exposed subjects, as observed in only two previous studies.[25,26] Of note, only 5 men (3 highly exposed and 2 not exposed) out of 1537 cases and 3 men (1 highly exposed and 2 not exposed) out of 1617 controls reported having been diagnosed with silicosis. These findings support silica carcinogenicity per se, against the still debated hypothesis of silicosis as necessary intermediate factor for lung cancer aetiology.[27–29] The exposed subjects in our study were principally employed in the construction sector (e.g. bricklayers), rather than in high-risk industries, such as mining

Table 3 Lung cancer risk for exposure to JEM carcinogens by main histological types for men in the EAGLE study, Lombardy, Italy, 2002–05[a]

		Adenocarcinoma		Squamous cell carcinoma		Small-cell carcinoma		
Carcinogen	**Controls, *N***	**Cases, *N***	**OR[c] (95% CI)**	**Cases, *N***	**OR[c] (95% CI)**	**Cases, *N***	**OR[c] (95% CI)**	***P*[b]**
Total	1617	582		459		157		
Asbestos								
Never[d]	1097	346	1.00	270	1.00	85	1.00	
Any	520	236	1.75 (1.37–2.23)	189	1.85 (1.40–2.43)	72	2.04 (1.38, 3.00)	
Low	448	202	1.76 (1.36– 2.29)	163	1.73 (1.29– 2.34)	65	1.92 (1.26, 2.92)	
High	72	34	1.67 (0.93–2.97)	26	1.34 (0.69– 2.63)	7	1.09 (0.40, 2.94)	
P-value			<0.001		0.002		0.03	0.65
Silica								
Never[d]	1363	480	1.00	322	1.00	111	1.00	
Any	254	102	0.94 (0.68–1.31)	137	1.66 (1.19–2.33)	46	2.03 (1.26–3.27)	
Low	226	94	0.97 (0.69–1.37)	118	1.64 (1.14–2.34)	40	2.11 (1.27–3.52)	
High	28	85	0.71 (0.30–1.70)	19	2.30 (1.09–4.86)	6	2.29 (0.81–6.51)	
P-value			0.56		0.001		0.003	0.03
Ni–Cr								
Never[d]	1216	421	1.00	291	1.00	105	1.00	
Any	401	161	1.15 (0.84–1.57)	168	1.47 (1.05–2.06)	52	0.98 (0.60–1.59)	
Low	328	127	1.13 (0.81–1.58)	124	1.31 (0.91–1.89)	34	0.79 (0.46–1.37)	
High	73	34	0.95 (0.55–1.63)	44	1.59 (0.90–2.81)	18	1.46 (0.68–3.15)	
P-value			0.84		0.06		0.69	0.23
PAH								
Never[d]	1235	447	1.00	331	1.00	112	1.00	
Any	382	135	0.75 (0.56–1.02)	128	0.97 (0.69–1.35)	45	1.01 (0.63–1.61)	
Low	321	103	0.71 (0.52–0.97)	83	0.81 (0.57–1.16)	30	0.87 (0.53–1.44)	
High	61	32	1.24 (0.66–2.36)	45	2.44 (1.25–4.76)	15	2.32 (0.94–5.73)	
P-value			0.28		0.34		0.48	0.12
DME								
Never[d]	994	379	1.00	259	1.00	97	1.00	
Any	623	203	0.77 (0.60–0.99)	200	1.04 (0.79–1.38)	60	0.65 (0.43–0.99)	
Low	500	162	0.80 (0.62–1.04)	162	1.09 (0.82–1.46)	45	0.67 (0.43–1.04)	
High	123	41	0.65 (0.41–1.02)	38	0.92 (0.55–1.53)	15	0.70 (0.35–1.41)	
P-value			0.03		0.94		0.11	0.44

DME, diesel motor exhausts; Ni–Cr, nickel and chromium compounds.
[a]*P* values were calculated from test for linear trend for never/low/high exposure.
[b]*P* values were calculated from test of homogeneity between ORs.
[c]OR calculated with unconditional logistic regression models, adjusted for area, age, smoking, number of jobs and for co-exposure of the other JEM carcinogens.
[d]Reference category: never exposed to the specific carcinogen.

and quarrying, as in most of the first occupational cohort studies.[27,28,30–33]

As a confirmation, when we excluded from the analysis the 328 cases and 254 controls that have ever held a job in the construction sector, only the ORs for any exposure to silica were slightly decreased (OR = 1.2; 95% CI: 0.83–1.62 instead of the original OR = 1.3; 95% CI: 1.02–1.68). Our findings emphasize the high public health impact of silica exposure, which is currently estimated the most common occupational exposure worldwide, with tens of millions of workers, particularly in the construction sector.[2] In Italy, 250 000 workers were reported to be exposed in the period 2000–03.[24]

Table 4 Lung cancer risk for the joint exposure to cigarette smoking and asbestos, silica and nickel–chromium for men in the EAGLE study, Lombardy, Italy, 2002–05

	Never smokers		Former smokers		Current smokers	
Carcinogen	**Ca/Co**	**OR[a] (95% CI)**	**Ca/Co**	**OR[a] (95% CI)**	**Ca/Co**	**OR[a] (95% CI)**
Asbestos						
Never	15/277	1.00[b]	424/500	14.25 (8.31–24.43)	466/270	35.67 (20.68-61.53)
Any	14/120	2.47 (1.15-5.31)	299/249	25.30 (14.51–44.12)	319/150	49.54 (28.18-87.08)
P^c-value			0.19			
Silica						
Never	24/347	1.00[b]	543/663	11.82 (7.67-18.23)	599/352	26.87 (17.34-41.63)
Any	5/50	1.41 (0.51-3.91)	180/136	18.94 (11.73-30.57)	186/68	44.98 (27.15-74.52)
P^c-value			0.94			
Ni–Cr						
Never	21/306	1.00[b]	496/597	11.97 (7.54-19.00)	524/312	26.73 (16.74-42.67)
Any	8/91	1.33 (0.57-3.12)	227/202	17.41 (10.66-28.43)	261/108	42.29 (25.54–70.04)
P^c-value			0.86			

Ca, cases; Co, controls; Ni–Cr, nickel and chromium compounds.
[a]Calculated with unconditional logistic regression models, adjusted for area, age and number of jobs.
[b]Reference category: never exposed to both carcinogen and smoking.
[c]$P_{interaction}$ values were calculated from 2-df log-likelihood ratio tests between the model with and without interaction term for joint exposure to smoking (never/former/current smoking status) and the specific carcinogen (never/any exposure).

The specificity of association of silica exposure with squamous and small-cell carcinomas, and not with adenocarcinoma, could only be evaluated in a few studies with enough power. A Canadian study found a risk pattern consistent with ours,[26] whereas a recent multicentric study from Central–Eastern Europe found increased ORs for all the three histological types.[25] Our results could in theory be explained by residual confounding by smoking, considering that these histological types are known to be strongly associated with tobacco exposure.[34] To rule out this possibility, we stratified the analyses by smoking status: the increased risk was evident among all smoking strata (although there were few exposed subjects especially among never smokers; data not shown), supporting the hypothesis of an independent effect of silica with respect to smoking.

We estimated a 1.18-fold increased risk for combined exposure to Ni and Cr among low-exposed workers (e.g. metal mechanics) instead of highly exposed workers in nickel refinery industries[35] and chromate production,[36] as previously reported. In addition, previous studies lacked detailed data on smoking exposure and could not adjust for co-exposure to other carcinogens. Only one similar study found an increased risk also at low levels, but for single Ni exposure.[37] Our approach of combining Ni and Cr exposures has been previously adopted because of the frequent simultaneous use of these carcinogens in most workplaces.[38]

We found a 1.64-fold increased risk for exposure to PAH only among highly exposed workers employed in metal basic industries, as in a recent large European multicentric study.[39] One study reported an increased risk also for any exposure to PAH,[40] but it did not adjust for co-exposure to other carcinogens (in particular asbestos), which in our study substantially decreased the risk estimates.

Our null result for any exposure to DME is consistent with other population-based studies,[41–43] but not all,[8,44] possibly because of misclassification of the 'non-exposed' subjects in our study due to the high background levels of DME in the urban areas. Unlike our study that includes mostly professional drivers (e.g. bus and taxi drivers), the majority of previous discordant occupational cohorts included highly exposed miners and railroad workers,[45–47] had inaccurate DME exposure assessment, scarce or null information on smoking, inadequate latency periods or failed to adjust for other carcinogens.[48–51]

A multiplicative effect for joint exposure to asbestos and smoking has been found in the majority of studies, even if a high variability of patterns is reported.[52,53] In contrast, to our knowledge, this is the first time that it has been found for smoking and silica. The few studies with enough lung cancer cases among never smokers reported a superadditive, but less than multiplicative interaction model.[25,26] For Ni–Cr, the comparison with previous studies is limited by the combined exposure variable used: patterns from multiplicative to additive were found for the single carcinogens.[35,37,54]

The PAFs estimated for any exposure to asbestos, silica and Ni–Cr with a JEM approach are higher

than that we previously reported of 4.9%.[6] This is an expected finding due to the higher sensitivity of the JEM as method of exposure assessment,[4] compared with job title approach, therefore more suitable to detect specific hazards across a large range of different job categories, as occur in a general population. In the literature, a wide PAF variability for these three carcinogens, between 1% and 40%, was reported,[2,19,55,56] probably because of differences in study design, exposure assessment methods or adjustment for confounders. Our industrial setting was also characterized by a low prevalence of high risk sectors (e.g. shipbuilding and railroad equipment manufacturing).[6] Although based on different numbers of carcinogens and sources for the risk estimates, our overall PAF (22.5%) was very similar to the overall PAF found in a recent study from UK (21.1%),[56] and higher than that found in France (12.5%).[55]

By applying our PAFs to the lung cancer incidence rates in males in Lombardy in 2005,[57] we estimated that 817 (95% CI: 569–1052), 257 (95% CI: 18–479), 316 (95% CI: 9–600) and 1016 (95% CI: 637–1355) lung cancer cases were attributable to occupational exposure to asbestos, silica, Ni–Cr and these three exposures combined, respectively. If we consider also the increased risk found for high exposure to PAH, corresponding to a PAF of 2.9% (95% CI: 0.1–5.9), there would be 131 additional potentially avoidable cases (95% CI: 5–266). These numbers sharply contrast with those officially reported to and compensated by the Italian Workers' Compensation Authority. For instance, in the period 1999–2004, only 399 work-related lung cancer cases (on average 66.5/year) were reported in Lombardy and about half of them compensated.[58]

The present study has a number of strengths: enrolment of incident cases and randomly sampled population controls, large sample size, elevated participation rates and face-to-face interviews by trained operators. Reliability of self-reported job history is considered good and not an important source of recall bias.[4]

The 'DOM-JEM' has unique qualities: it was developed blindly to case–control status to avoid potential differential exposure misclassification[7] by a team of trained experts with an excellent inter-rater agreement (between 77% and 95%). Moreover, it covers all the occupations and was also designed to have a high specificity to take into account the low exposure prevalence to occupational carcinogens in population-based studies, thus increasing the proportion of subjects correctly classified as unexposed, which can decrease potential misclassification bias.[4] The major drawback of the JEM approach is the possibility of non-differential exposure misclassification, due to the assignment of individual exposure to a specific carcinogen based on job title only.[9] Therefore, attenuation of the true association estimates and of exposure–response trends is likely.[59]

Another possible limitation of our study is recall bias. However, we expect the resulting misclassification to be mostly non-differential because we asked about occupations, not exposure to agents. Moreover, the coding of occupations was blind with respect to case–control status.

Although our detailed collection of smoking history allowed us to strictly control for smoking exposures, residual confounding from smoking cannot be completely ruled out. However, the likelihood of occurrence of substantial confounding by smoking is rare in occupational epidemiology.[60]

The lack of reliable risk estimates for women creates an underestimate of the true occupational lung cancer burden, but it is likely small, given the female minority in workplaces where the evaluated exposures occurred.[61]

Conclusion

In conclusion, our results provide strong evidence that past occupational exposure to asbestos, crystalline silica, nickel–chromium compounds and possibly PAH still causes a substantial proportion of lung cancer cases. Although in Italy asbestos use dropped before its ban by law in 1992, it continues to have the greatest impact on lung cancer burden. This result endorses the concern of many international groups currently campaigning for a global ban on all asbestos around the world.[62] Our findings support the need for policies aimed at strengthening environmental control measures and health surveillance at workplaces where dangerous exposures still exist.

Supplementary Data

Supplementary Data are available at *IJE* online.

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Conflict of interest: None declared.

KEY MESSAGES

- Occupational exposure to asbestos, silica and nickel–chromium compounds are associated with increased risk of lung cancer in men, even at low exposure levels.
- Occupational carcinogens are responsible for hundreds of lung cancer cases per year, in a general population of a developed country.
- Policies aimed at strengthening environmental control measures and health surveillance at workplaces are warranted.

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