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IJC
International Journal of Cancer

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Key words: lung neoplasms, case–control studies, bricklayers, occupational health, epidemiology
Additional Supporting Information may be found in the online version of this article.
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Grant sponsor: German Social Accident Insurance (DGUV); **Grant number:** FP 271; **Grant sponsors:** Canadian Institutes for Health Research and Guzzo-SRC Chair in Environment and Cancer, National Cancer Institute of Canada, Canadian Cancer Society, Occupational Cancer Research Centre, Workplace Safety and Insurance Board, Canadian Cancer Society, and Cancer Care Ontario; **Grant sponsor:** European Commission's INCO Copernicus program; **Grant number:** IC15-CT96-0313; **Grant sponsor:** European Union Nuclear Fission Safety Program; **Grant number:** F14P-CT96-0055; **Grant sponsors:** French Agency of Health Security (ANSES), Fondation de France, French National Research Agency (ANR), National Institute of Cancer (INCA), Fondation pour la Recherche Médicale, French Institute for Public Health Surveillance (InVS), Health Ministry (DGS), Organization for the Research on Cancer (ARC), and French Ministry of work, solidarity, and public function (DGT); **Grant sponsor:** Federal Ministry of Education, Science, Research, and Technology; **Grant number:** 01 HK 173/0); **Grant sponsor:** Federal Ministry of Science; **Grant number:** 01 HK 546/8; **Grant sponsor:** Ministry of Labour and Social Affairs; **Grant number:** IIIb7-27/13; **Grant sponsor:** Research Grants Council of the Hong Kong Special Administrative Region, China; **Grant number:** CUHK4460/03M; **Grant sponsors:** Environmental Epidemiology Program of the Lombardy Region, INAIL, Italian Association for Cancer Research, Region Piedmont, Compagnia di San Paolo, Lazio Region, Health Research Council of New Zealand, New Zealand Department of Labour, Lottery Health Research, Cancer Society of New Zealand; **Grant sponsor:** Polish State Committee for Scientific Research; **Grant number:** SPUB-M-COPERNICUS/P-05/DZ-30/99/2000; **Grant sponsors:** Instituto Universitario de Oncologia, Universidad de Oviedo, Asturias, Fondo de Investigacion Sanitaria (FIS) and Ciber de Epidemiologia y Salud Publica (CIBERESP), Swedish Council for Work Life Research and Swedish Environmental Protection Agency, Dutch Ministry of Health, Welfare and Sports, National Institute of Public Health and the Environment, and Europe Against Cancer Program, Roy Castle Foundation, and Intramural Research Program of the National Institutes of Health, National Cancer Institute, Division of Cancer Epidemiology and Genetics, Bethesda, Maryland.
DOI: 10.1002/ijc.28986
History: Received 21 Jan 2014; Revised 11 Apr 2014; Accepted 24 Apr 2014; Online 27 May 2014
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Bricklayers may be exposed to several lung carcinogens, including crystalline silica and asbestos. Previous studies that analyzed lung cancer risk among these workers had several study design limitations. We examined lung cancer risk among bricklayers within SYNERGY, a large international pooled analysis of case–control studies on lung cancer and the joint effects of occupational carcinogens. For men ever employed as bricklayers we estimated odds ratios (OR) and 95% confidence intervals (CI) adjusted for study center, age, lifetime smoking history and employment in occupations with exposures to known or suspected lung carcinogens. Among 15,608 cases and 18,531 controls, there were 695 cases and 469 controls who had ever worked as bricklayers (OR: 1.47; 95% CI: 1.28–1.68). In studies using population controls the OR was 1.55 (95% CI: 1.32–1.81, 540/349 cases/controls), while it was 1.24 (95% CI: 0.93–1.64, 155/120 cases/controls) in hospital-based studies. There was a clear positive trend with length of employment ($p<0.001$). The relative risk was higher for squamous (OR: 1.68, 95% CI: 1.42–1.98, 309 cases) and small cell carcinomas (OR: 1.78, 95% CI: 1.44–2.20, 140 cases), than for adenocarcinoma (OR: 1.17, 95% CI: 0.95–1.43, 150 cases) (*p*-homogeneity: 0.0007). ORs were still elevated after additional adjustment for education and in analyses using blue collar workers as referents. This study provided robust evidence of increased lung cancer risk in bricklayers. Although non-causal explanations cannot be completely ruled out, the association is plausible in view of the potential for exposure to several carcinogens, notably crystalline silica and to a lesser extent asbestos.

What's new?
In their work, bricklayers can be exposed to various airborne carcinogens, including crystalline silica and asbestos. Previous studies of cancer risk have not accounted for full employment history or smoking status, and failed to establish a firm relationship between bricklaying and lung cancer. In this study, the authors used data from the largest collection of case-control studies on lung cancer with complete occupational and smoking history existing today, the SYNERGY project. They found clear evidence that lung cancer risk increases in proportion to the length of time spent working as a bricklayer, paving the way for better protection and compensation for those in this occupation.

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Of the 11 million workers in the construction industry in the European Union (1990–1993), it has been estimated that more than half were exposed to carcinogenic agents.[1] The most common carcinogenic exposure was crystalline silica in the form of quartz dust (19% of the workforce exposed), followed by diesel fumes (6%) and asbestos (5%). Less frequent exposures included cadmium (0.3%), chromium (0.2%) and nickel (0.3%).[2] The impact of this industrial sector on the total lung cancer burden is estimated to be substantial.[3]

Several jobs within the construction sector are known (insulators and pipe coverers, roofers and asphalt workers using coal-tar, painters, truck drivers and operators of excavating machines) or suspected (carpenters) to increase lung cancer risk.[4–6] Bricklayers represent a large proportion of construction workers in several countries. Increased lung cancer risks were reported for bricklayers in several studies.[7–20] However, most of these studies were registry-based, general population studies or cohort studies using routinely collected information and thus had important drawbacks, including lack of complete job history information and/or smoking data,[7–12,17,18,20] or availability of only limited smoking information.[13,17] Also the few case–control studies that collected smoking information through interviews had study design limitations. In particular, only one study included (partly) controls selected from the general population (the other two being based on controls selected from pathology or cancer registry records).[16] Moreover, two had very small sample sizes leading to imprecise odds ratios estimates;[15,16] only one study had a fair number of bricklayers.[14] For these reasons, a firm association between working as a bricklayer and lung cancer risk has not yet been established. Lung cancer among bricklayers is therefore not recognized as an occupational disease in most countries (unless exposure to asbestos or specific tasks with high exposure to crystalline silica are clearly documented) and the affected workers are not compensated.

To address this important public health issue, we studied the lung cancer risk for bricklayers within the SYNERGY project, a large international pooled analysis of case–control studies on the joint effects of occupational carcinogens in the development of lung cancer. SYNERGY represents today the largest collection of case–control studies on lung cancer with complete occupational and smoking information. Hence, it provides a unique opportunity to validly assess whether a lung cancer excess exists among bricklayers while taking into account major potential confounders, including smoking, socio-economic status and work in other occupations. Further, its large sample size allows the examination of the pattern of risk with length of exposure and by lung cancer histology.

Material and Methods

Study design

The SYNERGY project (http://SYNERGY.iarc.fr) pooled lung cancer case–control studies from 13 European countries, Canada, Hong Kong and New Zealand. Its primary objective is to study the joint effects of exposure to occupational lung carcinogens including asbestos, crystalline silica, polycyclic aromatic hydrocarbons and nickel and chromium compounds. SYNERGY currently includes 16 population- or hospital-based case–control studies which collected lifetime occupational and smoking history and a cohort-nested case–control study (Supporting Information Tables S1 and S2). The occupational data were coded using the International Standard Industrial Classification of All Economic Activities Rev. 2 (ISIC) and the 1968 International Standard Classification of Occupations (ISCO).[4,5] Ethical approvals were obtained in accordance with legislation in each country and by the Institutional Review Board at the International Agency for Research on Cancer (IARC).

The pooled dataset used in this study included 34,139 men (15,608 cases and 18,531 controls) recruited in 1985–2010 (Supporting Information Tables S1 and S2). The multicenter study INCO, coordinated by IARC, included seven studies in Central and Eastern Europe and United Kingdom. They were considered as individual studies in the analyses, for a total of 22 studies/centers. The majority of controls (14,519 or 78.3%) were sampled from general population lists of the respective study bases. Overall, the response rate was higher for cases (81%) than for controls (67%), with large variability across studies. Information was predominantly collected by interviews with the subjects themselves. Next-of-kin respondents were accepted in five studies. Face-to-face interviews were conducted for nearly 90% of the subjects.

Statistical analysis

We analyzed lung cancer risk for bricklayers (ISCO code 9-51.20). Out of 8,904 women within the SYNERGY database, only 6 had ever been employed as bricklayers. Therefore, we restricted statistical analyses to men. For subjects ever employed as bricklayers we calculated odds ratios (OR) and 95% confidence intervals (CI) with unconditional logistic regression models similar to those used in other SYNERGY studies. All models contained the covariates study (22 centers) and log(age). To adjust for cigarette smoking we used the following variables: ever cigarette smoker (yes/no), log(1 + pack-years), time since quitting cigarette smoking (five categories, 0 for never and current smokers, 2−7, 8−15, 16−25, $\geq$26 years before interview/diagnosis). We also adjusted for smoking (ever/never) of other forms of tobacco only (cigars and pipe). To take into account exposure to lung carcinogens in other jobs we adjusted for ever employment in occupations known (so called "list A") or suspected ("list B") to be associated with lung cancer. Precise definitions of the industry/occupations in the lists and the related ISIC/ISCO code can be found elsewhere.[4,5] Briefly, list A includes mining and quarrying, iron and steel founding, metal workers, ceramic, refractory bricks, and granite production, asbestos production, shipyard and railroad manufacturing, insulators and pipe coverers, roofers, asphalt workers, coke plant and gas production and painters. Because of the recent inclusion of diesel engine exhausts among lung carcinogens,[6] we included in list A also bus and truck drivers and operators of excavating machines. List B includes butchers and meat workers, leather tanners and processors, carpenters, printing, rubber manufacture, glass production, motor vehicle manufacturing and repair, welders, railroad workers, filling station attendants and launderers. Subjects ever exposed to

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both list A and B occupations were classified in list A, so that the variable had the following values: 0 (never worked in occupations in list A or B), 1 (ever employed in list B but never in list A occupations) and 2 (ever employed in list A occupations). When not otherwise specified, the ORs reported in this article were obtained using the model adjusted for center, age, smoking and lists A/B.

We performed three sets of analyses by length of employment as bricklayers: (*i*) treating it as a categorical variable (<10, 10–19, 20–29, 30–39, ≥40 years); (*ii*) using restricted cubic splines (with knots at 10th, 25th, 50th, 75th and 90th percentiles of length of employment, log-transformed) and (*iii*) using a continuous log-transformed variable.[21] We calculated tests for linear trend for categorical length of employment and the OR for continuous length of employment either in the whole population or among bricklayers only: the aim of the latter analysis was to verify if the trend of lung cancer risk was dependent on the inclusion of the zero exposure category (never bricklayers).[22, pp. 316–317]

We evaluated risk for the main histologic types with polytomous (multinomial) logistic regression models.[22, pp. 413–414] In occupational cancer studies the need for adjustment for socioeconomic status (SES) is controversial and it is often advisable to present both crude and SES-adjusted estimates.[23] Therefore, we also provided: (*i*) ORs additionally adjusted for educational level (as a surrogate for SES) and (*ii*) ORs obtained when using as reference subjects ever employed in other blue collar jobs, defined by the following ISCO codes: 5–5 (building caretakers, charworkers, cleaners and related workers), 5–6 (launderers, dry-cleaners and pressers), 5–81 (firefighters), 6–28 (farm machinery operators), 6–31 (loggers) and all jobs (with the obvious exception of bricklayers) within the major group 7/8/9 (production and related workers, transport equipment operators and labourers).[4]

To take into account possible heterogeneity in job coding of "bricklayers" across study centers we performed an analysis by combining in a single category the ISCO code 9-51.20 ("Bricklayers"), and the less-specific codes 9-51.90 ("Other bricklayers, stonemasons and tile setters"), 9-59.10 ("Housebuilders") and 9-59.90 ("Other construction workers").

Meta-analytic and meta-regression techniques were used to visualize study-specific results, assess heterogeneity and to evaluate dependence of log(OR) on study characteristics, including study design, response rates, recruitment or job history periods and study size.[24] In these analyses, only studies for which there were enough cases and controls among bricklayers to calculate the OR could be included (Supporting Information Table S1). To detect asymmetry in the distribution of study-specific log(ORs) around the overall meta-analytic estimate we used the Egger's test. This test, which can be viewed as a statistical analogue to the funnel plot, determines whether the intercept deviates significantly from zero in a regression of the standardized effect estimates against their precision. Although the Egger's test (like a funnel-plot) is mainly known and used to detect publication bias in meta-analyses of published studies, an asymmetry of study-specific estimates may, in general, derive from other types of problems, including the presence of studies with small sample sizes.[24]

To quantify the confounding bias from cigarette smoking in estimating either the crude OR for bricklayers or the crude relative risk excess (OR − 1),[22, pp. 53,54] we used the following two formulas[22, p. 261]:

$$\text{Bias (\%) in crude OR} = 100\times\frac{(\text{OR}_{\text{crude}} - \text{OR}_{\text{adj}})}{\text{OR}_{\text{adj}}};$$

$$\text{Bias (\%) in crude OR excess} = 100\times\frac{[(\text{OR}_{\text{crude}} - 1) - (\text{OR}_{\text{adj}} - 1)]}{(\text{OR}_{\text{adj}} - 1)},$$

where OR_{crude} is the OR adjusted for study center, age, smoking of other types of tobacco only and lists A/B, and OR_{adj} is the OR additionally adjusted for lifetime cigarette smoking history (ever/never, pack-years and time since quitting).

To evaluate the modifying effect of smoking we performed a number of additional analyses. First, we calculated lung cancer risk only among never cigarette smokers. Second, we evaluated the joint effect (interaction) of working as a bricklayers and cigarette smoking by fitting a unique logistic model including the covariates: bricklayer (ever/never), cigarette smoking (ever/never), study center, log(age), smoking of other types of tobacco only (ever/never) and occupation in lists A/B. Then we evaluated the interaction on the multiplicative scale by adding an interaction term (bricklayer × smoking) and by calculating the likelihood ratio test between the two nested models (with and without interaction).[22, pp. 402–407] A similar approach was used to evaluate the modifying effect of exposure in lists A/B occupations. To assess the bricklayers-smoking interaction on the additive scale we calculated the relative excess risk due to interaction (RERI),[25] sometimes referred to as the interaction contrast ratio (ICR).[22, pp. 298–299] RERI > 0 indicates a more than additive (super-additive) interaction. Confidence limits for RERI were calculated using the method proposed by Zou.[26] Finally, we explored the modifying effect of cigarette pack-years by fitting a joint model to obtain ORs for length of employment (dichotomized as <20 and ≥20 years because of small numbers) stratified by cigarette pack-years in three categories: never cigarette smokers and light smokers (<10 pack-years) together; 10 to <35 pack-years; and ≥35 pack-years. ORs were adjusted for center, log(age), smoking of other tobacco products only, years since quitting cigarette smoking and occupation in lists A/B.

Statistical analyses were performed with Stata 13 (StataCorp. 2013. College Station, TX: StataCorp LP.).

Results

Study population

Out of 15,608 cases, 695 (4.5%) had ever been working as a bricklayer. Among the 18,531 controls, 469 were bricklayers (2.5%). In most studies, cases and controls were matched for age,

Table 1. Selected characteristics of male lung cancer cases and controls included in the pooled analyses on lung cancer risk among bricklayers, the SYNERGY study, 1985–2010

	Ever bricklayers				Never bricklayers				All			
	Cases		Controls		Cases		Controls		Cases		Controls	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
All subjects	695	100	469	100	14,913	100	18,062	100	15,608	100	18,531	100
Age (years)												
Mean (SD)	62.5	(9.0)	63.0	(9.3)	62.7	(9.0)	62.2	(9.5)	62.7	(9.0)	62.2	(9.5)
Cigarette smoking												
Never	15	2.2	107	22.8	647	4.3	5,194	28.9	662	4.2	5,301	28.6
Former (≥2 years)	336	34.0	230	49.0	5,186	34.8	7,859	43.5	5,422	34.7	8,089	43.6
Current	442	63.6	131	27.9	8,956	60.0	4,867	26.9	9,398	60.2	4,998	27.0
Unknown	2	0.3	1	0.2	124	0.8	142	0.8	126	0.8	143	0.8
Cigarette pack-years												
Mean/Median (SD)	45.2/42.0	(27.7)	23.3/18.0	(24.2)	42.4/38.3	(29.0)	20.2/13.2	(24.1)	42.6/38.5	(28.9)	20.3/13.5	(24.1)
Other tobacco only												
Ever	6	0.9	12	2.6	188	1.3	558	3.1	194	1.2	570	3.1
Education												
None	37	5.3	21	4.5	404	2.7	242	1.3	441	2.8	263	1.4
Some primary	186	26.8	97	20.7	2,975	19.9	2,538	14.0	3,161	20.3	2,635	14.2
Primary/some secondary	378	54.4	263	56.1	6,598	44.2	7,078	39.2	6,976	44.7	7,341	39.6
Secondary/some college	69	9.9	71	15.1	2,577	17.3	4,170	23.1	2,646	17.0	4,241	22.9
University	10	1.4	13	2.8	1,456	9.8	3,066	17.0	1,466	9.4	3,079	16.6
Unknown	15	2.2	4	0.8	903	6.1	968	5.4	918	5.9	972	5.3
Ever employed in list A/B[1]												
No	465	66.9	344	73.3	9,158	61.4	12,697	70.3	9,623	61.6	13,041	70.4
List B	78	11.2	26	5.5	2,073	13.9	2,185	12.1	2,151	13.8	2,211	11.9
List A	152	21.9	99	21.1	3,682	24.7	3,180	17.6	3,834	24.6	3,279	17.7
Lung cancer morphology												
Squamous cell carcinoma	309	44.5			6,105	40.9			6,414	41.1		
Small cell carcinoma	140	20.1			2,286	15.3			2,426	15.5		
Adenocarcinoma	150	21.6			3,864	25.9			4,014	25.7		
Other/unknown	96	13.8			2,658	17.8			2,754	17.6		

List A/B, occupations known (list A) or suspected (list B) to be associated with lung cancer; SD, standard deviation.
[1]Subjects with previous employment in occupations categorized in list A and B were assigned to list A.

therefore mean age was quite similar between cases and controls, both among bricklayers and non-bricklayers (Table 1). Compared to other subjects, bricklayers had smoked more cigarettes, had lower education level and had been less frequently employed in list B occupations. Smokers of other types of tobacco only (cigars and pipe) were very few. Among bricklayers there was a slightly lower frequency of employment in list A occupations for cases and higher for controls. Squamous cell and small cell carcinomas were more frequent among bricklayers than in the other subjects.

Smoking-adjusted lung cancer risk for bricklayers

The OR for ever working as a bricklayer adjusted for center, age, smoking and list A and B occupations was 1.47 (95% CI: 1.28–1.68) (Table 2). After adjustment for education the OR was 1.32 (95% CI: 1.14–1.52). Using as reference non-bricklayer blue collar workers, the OR was 1.37 (95% CI: 1.19–1.57). There were clear positive trends of lung cancer risk by categories of length of employment as a bricklayer, with some decrease after 40 years. The restricted cubic spline plots (Fig. 1) show a gradual increase of lung cancer risk until about 25 years and a plateau afterwards. However, in the analyses using continuous length of employment (log-transformed) ORs ranged from 1.14 to 1.19 (Table 2) with no evidence of departure from linearity ($p > 0.28$ for the quadratic and $p > 0.63$ for the cubic components of length of employment). The slopes were even higher when analyzing

Table 2. Lung cancer risk among bricklayers, the SYNERGY study, 1985–2010

	Cases	Controls	OR1	(95% CI)	OR2	(95% CI)	OR3	(95% CI)
All subjects	15,608	18,531						
Never bricklayers	14,913	18,062	1.00	(Reference)	1.00	(Reference)		
Never bricklayers, blue collars	11,750	12,275					1.00	(Reference)
Ever bricklayers	695	469	1.47	(1.28–1.68)	1.32	(1.14–1.52)	1.37	(1.19–1.57)
Length of employment as bricklayers								
<10 years	278	225	1.20	(0.98–1.47)	1.10	(0.90–1.36)	1.13	(0.92–1.38)
10–19 years	111	63	1.55	(1.09–2.20)	1.37	(0.96–1.94)	1.43	(1.01–2.03)
20–29 years	88	55	1.73	(1.17–2.56)	1.53	(1.03–2.26)	1.60	(1.08–2.37)
30–39 years	99	45	2.43	(1.61–3.66)	2.12	(1.40–3.20)	2.24	(1.48–3.37)
≥40 years	89	55	1.81	(1.22–2.69)	1.58	(1.06–2.35)	1.68	(1.13–2.49)
Unknown	30	26	–	–	–	–	–	–
Test for linear trend (*p*-value)			<0.001		<0.001		<0.001	
Test for linear trend among bricklayers only (*p*-value)			0.005		0.016		–[1]	
Length of employment as bricklayers, log (years)								
Among all subjects	15,578	18,505	1.19	(1.13–1.25)	1.14	(1.08–1.20)	1.16	(1.10–1.22)
Among bricklayers only	665	443	1.26	(1.08–1.47)	1.22	(1.04–1.44)	–[1]	
Lung cancer morphology								
Squamous cell carcinoma	309		1.68	(1.42–1.98)	1.45	(1.22–1.72)	1.53	(1.29–1.81)
Small cell carcinoma	140		1.78	(1.44–2.20)	1.56	(1.26–1.94)	1.61	(1.30–2.00)
Adenocarcinoma	150		1.17	(0.95–1.43)	1.11	(0.91–1.37)	1.12	(0.91–1.37)
Test of homogeneity (*p*-value)			0.0007		0.017		0.005	

Lists A/B, occupations known (list A) or suspected (list B) to be associated with lung cancer; CI, confidence interval; OR1, odds ratio adjusted for study center, age, smoking, and list A/B occupations; OR2, odds ratio adjusted for study center, age, smoking, lists A/B occupations, and education; OR3, odds ratio adjusted for study center, age, smoking, and lists A/B occupations, with blue collar workers as reference.
[1]Same as OR1 analysis.

length of employment among bricklayers only. There was an evident association between working as a bricklayer and small cell and squamous cell carcinoma, while the ORs for adenocarcinoma were much smaller (Table 2).

Smoking-adjusted lung cancer risk for bricklayers by study center and type of controls

Study-specific smoking-adjusted ORs and meta-analytic estimates, stratified by type of controls, are shown in Figure 2. Fifteen studies, eight using population[27–34] and seven using hospital/mixed controls[31,35,36] contributed to the overall estimates for bricklayers. The overall fixed- and random-effect OR estimates were 1.44 and 1.45, virtually identical to the maximum likelihood OR (1.47) obtained from logistic regression on the pooled data. The funnel plot (not shown) was rather symmetric and the Egger's test ($p = 0.45$) confirmed the visual impression of no asymmetry of study-specific log(ORs) around the overall estimate. Two studies (AUT-Munich and EAGLE) included 55.4% of bricklayers. In logistic regressions, exclusion of AUT-Munich gave an OR of 1.53 (95% CI: 1.30–1.80), and excluding EAGLE an OR of 1.43 (95% CI: 1.22–1.68).

In population-based studies (Fig. 2, top half) the meta-analytic ORs for bricklayers were 1.52 (fixed-effect) and 1.65 (random-effect), while in studies using hospital/mixed controls (Fig. 2, bottom half) both ORs were 1.20 (p for homogeneity across study type = 0.20 from a meta-regression model).

In studies with population controls (Table 3) all logistic regression ORs were higher than in the overall analysis while showing very similar patterns. In analyses restricted to studies with hospital/mixed controls (Table 4), the overall ORs ranged from 1.18 to 1.24, lung cancer risk by length of employment showed an irregular pattern (with elevated ORs in the category <10 years and after 30 years), and elevated ORs were found for squamous cell and small cell carcinomas, not for adenocarcinoma.

Evaluation of confounding and effect modification by smoking

The overall OR for bricklayers adjusted for study center, age, smoking of other types of tobacco and occupations in lists A/B (not shown in tables) was 1.66 (95% CI: 1.47–1.88), against an OR also adjusted for lifetime cigarette smoking of 1.47 (Table 2). Hence, in this study not adjusting for cigarette smoking would have produced a confounding bias of the crude OR of +13% (= 100 × [1.66 − 1.47]/1.47), while in

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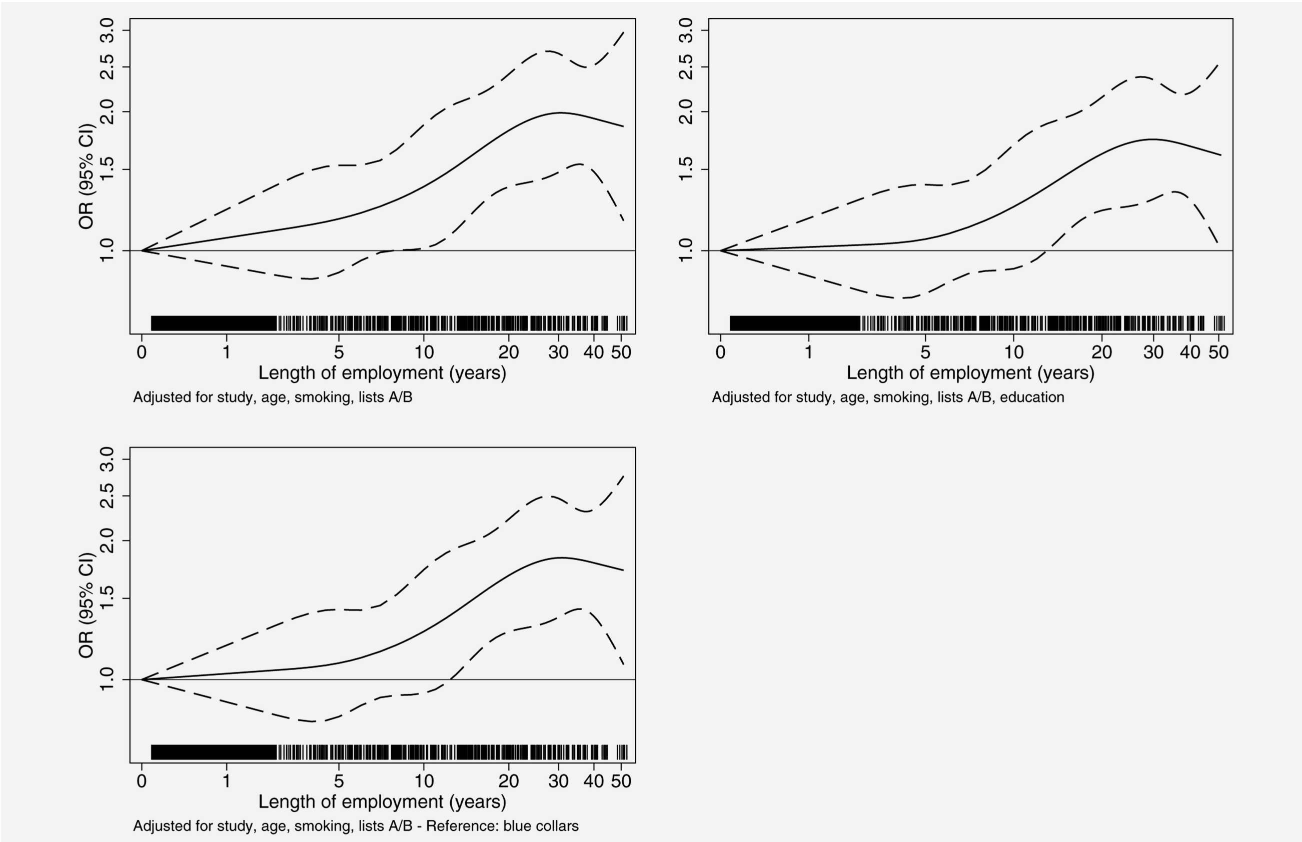

Figure 1. Association between lung cancer risk and length of employment as bricklayers using restricted cubic splines (knots at 10th, 25th, 50th, 75th and 90th percentiles of length of employment, log-transformed), the SYNERGY study, 1985–2010. Note: A/B, occupations known (list A) or suspected (list B) to be associated with lung cancer; CI, confidence interval; OR, odds ratio. Vertical bars close to the horizontal axis indicate lung cancer cases.

terms of crude excess OR the bias from smoking would have been +40% (= 100 × [0.66 − 0.47]/0.47).

The OR for bricklayers among the 5,963 never cigarette smokers was 1.46 (95% CI: 0.82–2.60, from 15 cases and 107 controls among bricklayers). A joint model containing the variables bricklayers, cigarette smoking (ever/never) and their interaction produced the following results: compared to never bricklayers-never cigarette smokers, the lung cancer OR for bricklayers who never smoked cigarette was 1.18, that for ever cigarette smokers never bricklayers was 11.5 and the OR for ever bricklayers ever cigarette smokers was 18.5 (Supporting Information Table S3). There was no indication of interaction on the multiplicative scale (the OR for the interaction term was 1.37 (95% CI: 0.76–2.45; $p = 0.28$). There was indication of super-additive interaction (RERI = 6.80, 95% CI: 4.36–9.62).

The relationship between length of employment as a bricklayer stratified by cigarette pack-years is shown in Supporting Information Table S4. The increasing trend of ORs with length of employment was evident in each stratum, including light smokers (0 to <10 pack-years). There was no indication of interaction between length of employment and pack-years on the multiplicative scale ($p = 0.86$).

Evaluation of confounding and effect modification by exposures to carcinogens in other occupations

Among those never employed in list A or B occupations the smoking-adjusted ORs for bricklayers (results not shown in tables) was 1.51 (95% CI: 1.28–1.78, from 465 cases and 344 controls among bricklayers). For those ever employed in list B occupations the OR for bricklayers was 2.40 (95% CI: 1.45–3.99, 78 cases and 26 controls among bricklayers). Finally, the OR for bricklayers was 1.13 (95% CI: 0.85–1.51, 152 cases, 99 controls), among subjects ever employed in list A occupations. Although there was statistical evidence that those three ORs were different (p-interaction = 0.03), in all the analyses the list A/B variable was treated as a confounder and not as a modifier for simplicity of presentation. In general, the confounding effect of lists A/B was small: for example, the OR for bricklayers not adjusted for lists A/B was 1.45 (95% CI: 1.26–1.66), instead of 1.47 (Table 2).

Discussion

In this study we found a smoking-adjusted increased lung cancer risk for bricklayers, with a clear positive association with length of employment. The association was stronger for

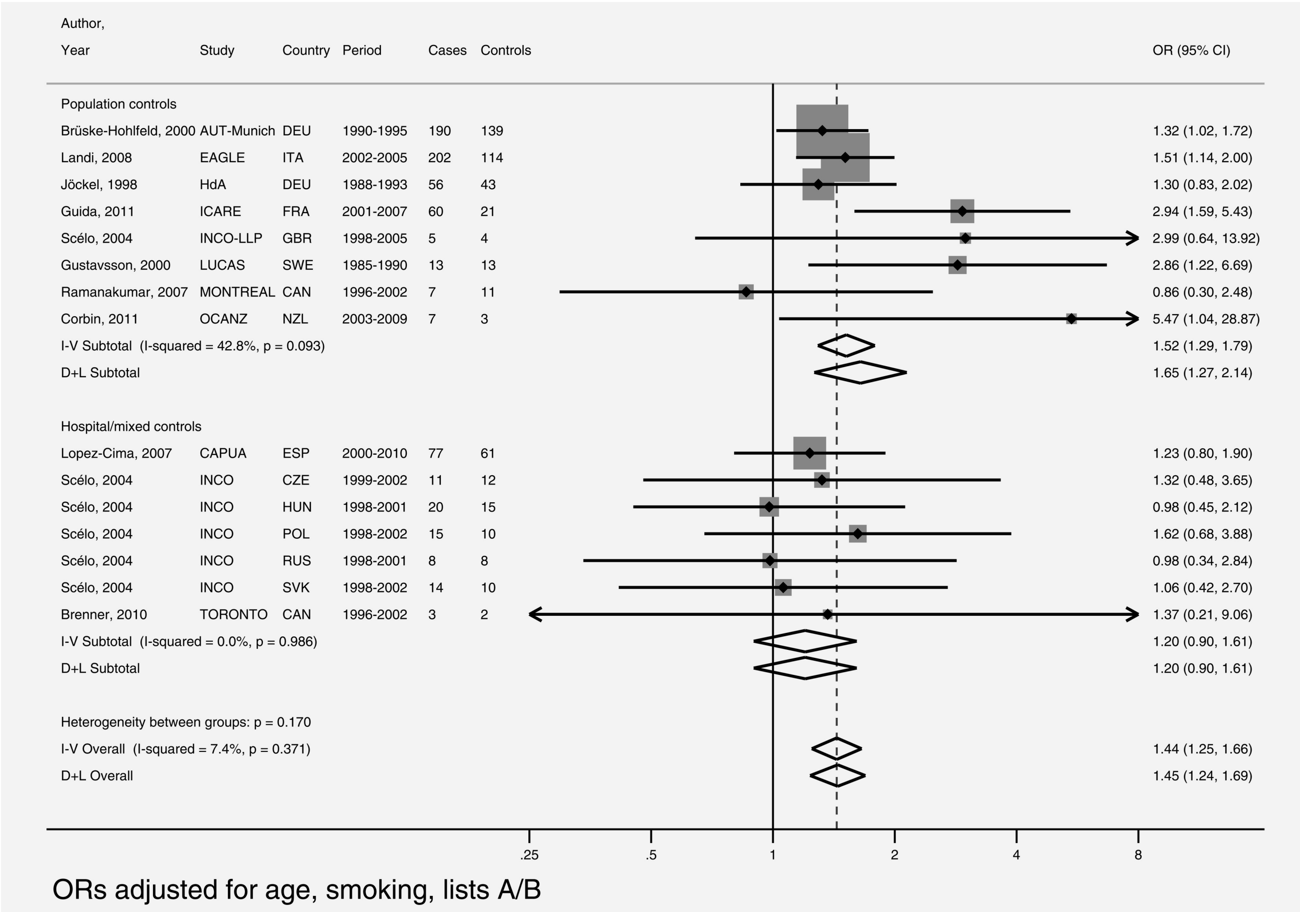

Figure 2. Study-specific and overall meta-analytic odds ratios (OR) for bricklayers, the SYNERGY study, 1985–2010. Note: A/B, occupations known (list A) or suspected (list B) to be associated with lung cancer; CI, confidence interval; D+L, DerSimonian and Laird random effect estimate; I–V, inverse–variance fixed effect estimate.

small cell and squamous cell lung carcinomas. These findings were confirmed after further adjustment for education and in analyses using as reference other blue collar workers.

Effect of study design

Study design had an important impact on OR estimates. Although statistically there was little heterogeneity in OR estimates ($p = 0.20$), in the eight population-based studies the ORs for bricklayers were 1.55 (adjusted for smoking and lists A/B), 1.35 (after further adjustment for education) and 1.43 (blue collar referents) and a clear positive trend for length of employment was found. The ORs were, respectively, 1.24, 1.18 and 1.19 in the seven studies using hospital/mixed controls (although clearly elevated ORs were found when analyzing squamous cell and small cell carcinomas), with no clear trend with length of employment. To explain these inconsistencies, we examined several subjects' and study characteristics.

Although most studies using hospital controls enrolled only patients with smoking-unrelated diseases and were careful in including several diagnostic groups (Supporting Information Table S2), the proportion of bricklayers among controls was slightly lower in population-based (349/14,519 = 2.4%) compared with hospital-based studies (120/4,012 = 3.0%) ($p = 0.036$). Therefore, the lower ORs in hospital-based studies can perhaps, at least in part, be attributed to the choice of control diseases. Response rates were higher in hospital-based studies. However, in meta-regression models we did not find evidence of associations of study-specific log(ORs) with response rates among cases ($p = 0.83$) or controls ($p = 0.84$), nor was there an association with case–control response ratios ($p = 0.59$). Also we did not find evidence of a relationship between log(ORs) and response rates (in cases, controls or both) within studies using population ($p = 0.92$, 0.25 and 0.32, respectively) or hospital/mixed controls ($p = 0.79$, 0.75 and 0.91, respectively). This would argue against lower response rates in population-based studies being a reason for the different OR estimates between hospital-based and population-based studies. Also, in meta-regression models we did not find associations between study-specific log(ORs) for bricklayers and average recruitment ($p = 0.60$) or job history periods ($p = 0.38$). Among studies using hospital/mixed controls, there were ORs close to unity in the three INCO studies performed in Hungary, Russia and Slovakia. These studies were small in size.

Table 3. Lung cancer risk among bricklayers in studies using population controls, the SYNERGY study, 1985–2010

	Cases	Controls	OR1	(95% CI)	OR2	(95% CI)	OR3	(95% CI)
All men	11,762	14,519						
Never bricklayers	11,222	14,170	1.00	(Reference)	1.00	(Reference)		
Never bricklayers, blue collars	8,816	9,512					1.00	(Reference)
Ever bricklayers	540	349	1.55	(1.32–1.81)	1.35	(1.15–1.59)	1.43	(1.22–1.68)
Length of employment as bricklayers								
<10 years	229	187	1.15	(0.92–1.43)	1.03	(0.82–1.29)	1.07	(0.86–1.34)
10–19 years	92	43	1.85	(1.23–2.78)	1.59	(1.06–2.39)	1.70	(1.13–2.55)
20–29 years	73	35	2.41	(1.51–3.87)	2.08	(1.30–3.34)	2.19	(1.37–3.52)
30–39 years	76	31	2.87	(1.77–4.66)	2.38	(1.47–3.85)	2.61	(1.61–4.24)
≥40 years	65	45	1.83	(1.17–2.86)	1.54	(0.98–2.41)	1.68	(1.07–2.63)
Unknown	5	8	–	–	–	–	–	–
Test for linear trend (*p*-value)			<0.001		<0.001		<0.001	
Test for linear trend among bricklayers only (*p*-value)			0.001		0.003		–[1]	
Length of employment as bricklayers, log(years)								
Among all subjects	11,757	14,511	1.23	(1.15–1.30)	1.17	(1.10–1.24)	1.19	(1.12–1.27)
Among bricklayers only	535	341	1.38	(1.16–1.65)	1.33	(1.11–1.60)	–[1]	
Lung cancer morphology								
Squamous cell carcinoma	233		1.77	(1.46–2.14)	1.47	(1.21–1.79)	1.60	(1.32–1.95)
Small cell carcinoma	109		1.86	(1.46–2.37)	1.58	(1.24–2.03)	1.66	(1.30–2.12)
Adenocarcinoma	120		1.23	(0.98–1.55)	1.15	(0.91–1.46)	1.18	(0.93–1.48)
Test of homogeneity (*p*-value)			0.004		0.06		0.02	

Lists A/B, occupations known (list A) or suspected (list B) to be associated with lung cancer; CI, confidence interval; OR1, odds ratio adjusted for study center, age, smoking, lists A/B; OR2, odds ratio adjusted for study center, age, smoking, lists A/B occupations, education; OR3, odds ratio adjusted for study center, age, smoking, lists A/B occupations, with blue collar workers as reference.
[1]Same as OR1 analysis.

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In summary, it appears that findings from hospital/mixed control studies can be explained by a combination of factors, including choice of control diseases, geographical location (possibly reflecting different exposure patterns) and study size. Although one could question the findings from population-based ORs, we feel the latter are preferable for a number of reasons. First, they are *a priori* superior in terms of representativeness of the study-base. Second, the results in population-based studies are statistically more precise, being based on a larger sample size (540 cases and 349 controls had ever worked as bricklayers, against 155/120 in hospital-based studies). Third, although population-based studies may suffer from selection bias due lower response rates, we did not find relationships between ORs and response rates in meta-regression analyses, nor after adjustment for education or when using blue collars workers as referents (see discussion on socio-economic status below). Therefore, selection bias is not a likely explanation for the stronger associations in population-based studies. Fourth, and most important, we found a clear positive exposure-response relationship in the population-based studies, which is regarded as a strong argument in favour of causality.[21]

Evaluation of potential information bias

With regard to possible information bias in our study, it is known that validity and reliability of self-reported job history obtained with an interviewer-administered questionnaire is generally good, especially for jobs held longer, and usually not a source of important recall bias.[37–39] In addition, in this study, blind coding of occupations minimized the possibility of differential bias, although a certain degree of non-differential misclassification is unavoidable, most likely leading to a bias towards the null. There are real differences in working practices in the construction sector across countries. Therefore, some difference in the proportions of bricklayers between geographical areas was expected. However, part of the heterogeneity may be due to different coding practices across study centers. For example, some of the studies that did not contribute cases/controls to the overall OR estimates probably coded some bricklayers under less specific ISCO codes, like 9–51.90 ("Other bricklayers, stonemasons and tile setters," 57/32 exposed cases/controls), 9–59.10 ("Housebuilders," 274/312 cases/controls) or 9–59.90 ("Other construction workers," 336/212 cases/controls). After combining bricklayers with those three codes the overall OR was

Table 4. Lung cancer risk among bricklayers in studies using hospital/mixed controls, the SYNERGY study, 1985–2010

	Cases	Controls	OR1	(95% CI)	OR2	(95% CI)	OR3	(95% CI)
All men	3,846	4,012						
Never bricklayers	3,691	3,892	1.00	(Reference)	1.00	(Reference)		
Never bricklayers, blue collars	2,934	2,763					1.00	(Reference)
Ever bricklayers	155	120	1.24	(0.93–1.64)	1.18	(0.89–1.58)	1.19	(0.90–1.59)
Length of employment as bricklayers								
<10 years	49	38	1.56	(0.95–2.57)	1.52	(0.92–2.52)	1.49	(0.90–2.45)
10–19 years	19	20	0.82	(0.40–1.69)	0.79	(0.38–1.62)	0.80	(0.39–1.64)
20–29 years	15	20	0.74	(0.35–1.58)	0.66	(0.31–1.42)	0.72	(0.34–1.54)
30–39 years	23	14	1.45	(0.67–3.16)	1.45	(0.66–3.19)	1.41	(0.65–3.06)
≥40 years	24	10	1.67	(0.72–3.91)	1.61	(0.68–3.80)	1.63	(0.69–3.81)
Unknown	25	18	–	–	–	–	–	–
Test for linear trend (*p*-value)			0.24		0.36		0.32	
Test for linear trend among bricklayers only (*p*-value)			0.93		0.86		–[1]	
Length of employment as bricklayers, log (years)								
Among all subjects	3,821	3,994	1.07	(0.96–1.19)	1.05	(0.94–1.17)	1.06	(0.95–1.18)
Among bricklayers only	130	102	0.87	(0.60–1.25)	0.90	(0.61–1.30)	–[1]	
Lung cancer morphology								
Squamous cell carcinoma	76		1.41	(1.01–1.97)	1.30	(0.93–1.83)	1.33	(0.95–1.87)
Small cell carcinoma	31		1.59	(1.02–2.48)	1.48	(0.94–2.32)	1.54	(0.99–2.41)
Adenocarcinoma	30		0.97	(0.63–1.51)	0.99	(0.63–1.54)	0.96	(0.62–1.50)
Test of homogeneity (*p*-value)			0.16		0.31		0.21	

Lists A/B, occupations known (list A) or suspected (list B) to be associated with lung cancer; CI, confidence interval; OR1, odds ratio adjusted for study center, age, smoking, lists A/B; OR2, odds ratio adjusted for study center, age, smoking, lists A/B occupations, education; OR3, odds ratio adjusted for study center, age, smoking, lists A/B occupations, with blue collar workers as reference.
[1]Same as OR1 analysis.

1.34 (95% CI: 1.21–1.48, 1,304 cases and 997 controls). Although lower because of inclusion of workers performing other tasks, this combined estimate was not very far from that (OR = 1.47) obtained when considering the specific code for bricklayers. Moreover, all other analyses yielded similar results, including a clear positive trend of risk ($p < 0.001$) with length of employment.

Evaluation of confounding by smoking and exposure to carcinogens in other occupations

In this study, there was positive confounding by cigarette smoking. However, it was taken into account by adjusting for detailed lifetime smoking history. Smoking was adequately modeled by including cumulative exposure (cigarettes pack-years) and time since quitting. Smokers of other types of tobacco only were very few and did not affect much the findings. We found conflicting evidence of an increased lung cancer risk among never cigarette smokers: the OR was 1.46 when fitting a model among never cigarette smokers only and 1.18 when fitting a joint bricklayers-smoking model using the whole dataset. However, the numbers of bricklayers who never smoked were rather small and ORs quite imprecise.

To test the robustness of our results we fitted many other methods to model smoking history available in the literature which use different combinations of cumulative exposure, intensity, duration and time since quitting: they gave almost identical overall ORs (ranging from 1.47 to 1.50). In both population- and hospital/mixed-based studies there were higher ORs for small cell and squamous cell carcinomas, the histologic types most strongly associated with smoking. This might be interpreted as a sign of residual confounding by smoking, a frequent concern in occupational lung cancer studies, although not always justified. However, this pattern is also compatible with the possibility that exposures occurring while working as a bricklayer are associated (like smoking) with different strength with the different lung cancer histological types. The clear positive trend of ORs by length of employment, either in adjusted analyses or in analyses stratified by pack-years, lends more support to the existence of true associations than to residual bias from smoking.

In this study, we were able to take into account exposures to carcinogens in other occupations, even though their confounding effect was small.

Evaluation of effect of socio-economic status

Adjustment for SES is usually advocated for two main reasons[23]: (*i*) to reduce non-response bias, because participation is often associated with SES; and (*ii*) to reduce positive confounding from SES-related life-style factors. Conversely, SES adjustment (or restriction of analysis to blue collars workers) may introduce a negative bias if other occupational exposures cause the cancer under study and if these exposures are strongly correlated with the factor under investigation. This is sometimes referred to as over-adjustment. Notwithstanding the controversial validity of this argument, the ORs adjusted for education or obtained from analyses restricted to blue collar workers were still increased and the positive trends for length of employment were still evident.

Lung cancer risk by length of employment

Although the statistical relationship between lung cancer log(OR) and length of employment as a bricklayer was compatible with a linear increase, we observed a drop in ORs after 40 years (in categorical analyses) and a plateau after about 25 years (in spline analyses). This phenomenon has been repeatedly noted in several occupational epidemiology studies dealing with (but not exclusively) carcinogens. Although several possible explanations have been proposed (*e.g.*, mismeasurement of high exposures, saturation of metabolic pathways, depletion of susceptible individuals and bias resulting from the healthy worker survivor effect), the issue is still unresolved.[21]

Literature findings

Several studies reported relative risk estimates for lung cancer among bricklayers (Supporting Information Table S5). Three studies showed smoking-unadjusted proportionate mortality ratios (PMR) of 1.18, 1.20 and 1.34.[7,18,20] However, in two of them the relative risk was lower (1.09) when blue collar workers were used as referents[20] or mortality odds ratios (MOR) were calculated.[7] Three registry-based case–control studies reported excesses of lung cancer among bricklayers,[8,13,17] but they suffered from a number of limitations, including absence of smoking data[8] (or availability of only limited information),[13,17] lack of complete job history[8,17] and small sample size.[13,17] In Nordic countries, the nationwide smoking-unadjusted standardized incidence ratio (SIR) in 1971–1991 for bricklayers was 1.19.[9] In a recent (1961–2005) update the estimated SIR was 1.25.[11] A nationwide study in Switzerland found a smoking-unadjusted standardized mortality ratio (SMR) of 2.12 and a PMR of 1.58 for masons.[10] A large cohort study in Ontario found a smoking-unadjusted SMR of 1.30 in bricklayers, which became 1.53 when excluding places where refractory materials were used.[12] Complete job and smoking histories were collected by interview in three case–control studies: the OR estimates ranged from 1.3 to 2.7.[14–16] Two of those studies were very small in size.[15,16] The only case–control study with a fair sample size included only patients with adenocarcinoma of the lung and hospital controls.[14] The relationship with length of employment and time since first employment was examined in a few studies,[12–14] and a positive association reported in two.[12,14]

Exposure to lung carcinogens for bricklayers

Bricklayers may have been exposed to several known or suspected lung carcinogens. The occurrence of pleural cancer excesses in construction workers underlines the importance of exposure to asbestos in this sector.[3] However, asbestos exposure was most probably intermittent as it occurred during specific tasks only (*e.g.*, insulation, demolition and building renewal). Indeed, a relatively small fraction (5%) of workers in the construction industry in Europe were considered exposed to asbestos.[2] Hexavalent chromium (CrVI) and nickel compounds are contained in cement/concrete, but the estimated fraction of exposed workers in Europe was very low (<1%).[2] Moreover, the levels of exposure inhalable cement dust are not usually very high among bricklayers.[40]

The predominant past (and present) exposure for bricklayers is crystalline silica in the form of quartz dust, which concerns a substantial fraction (almost 20%) of the workforce in the construction industry[2] and occurs frequently during several tasks (concrete mixing, cutting, drilling, sandblasting, demolishing and cleaning).[41,42] Moreover, industrial hygiene assessments in several countries reported exposure concentrations of respirable crystalline silica for bricklayers above the exposure limit of 0.025 mg/m^3 (respirable quartz)[42–53] currently recommended by the American Conference of Governmental Industrial Hygienists (ACGIH). A quantitative job-exposure matrix developed for SYNERGY estimated for bricklayers exposures to respirable crystalline silica in 1998 ranging from 0.02 to 0.07 mg/m^3.[54] In the SYNERGY study six centers (AUT-Munich, CAPUA, EAGLE, HdA, ICARE, INCO, including more than 20,000 subjects in total)[27–31,35] had collected data on pneumoconiosis: 78 cases (12 bricklayers) and 39 controls (5 bricklayers) reported to have been diagnosed with silicosis. Radiographic abnormalities and low-grade silicosis (detected through high-resolution CT) have also been reported among construction workers exposed to quartz-containing dust in other studies.[55] Reduction of exposure to quartz is regarded as a priority for bricklayers.[56]

Conclusion

We found an increase in lung cancer risk among bricklayers, with a clear positive association with length of employment. Although non-causal explanations cannot be completely ruled out, the association is plausible in view of the potential for exposure to several carcinogens, notably crystalline silica. Exposure to respirable crystalline silica-containing dust also concerns other workers in the construction industry. The large number of workers in the construction industry suggests that a focus on the work environment, in particular the monitoring and control of respirable crystalline silica-containing dust, may provide a further opportunity for lung cancer prevention.

Acknowledgements

The authors thank Véronique Luzon (IARC) for pooling and managing data.

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