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Occupational Lung Cancer Risk for Men in Germany: Results from a Pooled Case-Control Study

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Occupational exposures such as crystalline silica, diesel engine exhaust, polycyclic aromatic hydrocarbons, and man-made mineral fibers are strongly suspected to increase lung cancer risk. Two case-control studies in Germany conducted between 1988 and 1996 were pooled for a joint analysis. A total of 3,498 male cases and 3,541 male population controls, frequency matched for age and region, were included in the study. The lifelong history of all jobs and industries was coded and occupational exposures were evaluated by expert rating. Odds ratios, crude and adjusted for smoking and asbestos exposure, were calculated by conditional logistic regression. Job-related evaluation showed a statistically significant increased odds ratio adjusted for smoking among farmers; forestry workers, fishermen, and livestock workers; miners and quarrymen; chemical processors; cabinet makers and related wood workers; metal producers and processors; bricklayers and carpenters; road construction workers, pipelayers and well diggers; plasterers, insulators, and upholsterers; painters and lacquerers; stationary engine and heavy equipment operators; transport workers and freight handlers; and service workers. With regard to specific occupational exposures, elevated odds ratios (OR) (95% confidence intervals (CI)) for lung cancer risk adjusted for smoking and asbestos exposure were observed for man-made mineral fibers (OR = 1.48, 95% CI 1.17, 1.88); crystalline silica (OR = 1.41, 95% CI 1.22, 1.62); diesel engine exhaust (OR = 1.43, 95% CI 1.23, 1.67); and polycyclic aromatic hydrocarbons (OR = 1.53, 95% CI 1.14, 2.04). The risk of asbestos exposure, adjusted for smoking was also increased (OR = 1.41, 95% CI 1.24, 1.60). *Am J Epidemiol* 2000;151:384–95.

asbestos; case-control studies; lung neoplasms; mineral fibers; polycyclic hydrocarbons, aromatic; silicon dioxide; vehicle emissions

Lung cancer is the most frequent neoplasm among men in North America and in Europe, and it is rapidly increasing among women (1–3). Tobacco smoking as a cause of lung cancer has been conclusively established (4) as the main determinant of lung cancer incidence in both males and females. A number of occupational exposures have been shown to cause lung cancer (e.g., see references 5–8). Among these exposures are asbestos, radon, and various metals and/or their compounds: arsenic, chromium, nickel, and beryllium. Other suspected or recognized risk factors of lung cancer include indoor (9, 10) and outdoor air pollution (11, 12), and a family history of lung cancer (13, 14). None of these factors appear to be associated with relative risks as high as those observed with smoking. Because smoking is such a strong risk factor for lung cancer, its control as a potential confounder becomes extremely important. In general, cohort studies do not provide information on smoking detailed enough to allow for accurate adjustment in the analysis. Although case-control studies are superior in this respect, they usually suffer from small numbers, because study subjects are dispersed too thinly over a multitude of job and industry categories representing occupational exposures. We had the opportunity to overcome this disadvantage by combining two large case-control studies with similar study design and nearly identical questionnaire to estimate lung cancer risk for various

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Abbreviations: BaP, benzo[a]pyrene; CI, confidence interval; DEE, diesel engine exhaust; IARC, International Agency for Research on Cancer; JEM, job exposure matrix; MMMF, man-made mineral fibers; OR, odds ratio; PAH, polycyclic aromatic hydrocarbons; RR, relative risk.

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suspected occupational risk factors as: man-made mineral fibers (MMMF), crystalline silica, diesel engine exhaust (DEE), and polycyclic aromatic hydrocarbons (PAH) from combustion of organic materials. This paper is intended to present an overview of the methods applied and the most important findings. The above-mentioned specific exposures and such special aspects as, for example, occupational exposures in very young lung cancer patients (15) and in females (16) are addressed in separate papers.

MATERIALS AND METHODS

Study design

To investigate the influence of occupational exposures on lung cancer risk in Germany, two case-control studies were pooled for a joint analysis. One of the studies, the BIPS Study on lung cancer and occupational risk factors (17, 18) by the Bremen Institute for Prevention Research and Social Medicine was carried out between 1988 and 1993 in Bremen, the area surrounding Bremen, and the Frankfurt/Main area. It comprised 1,004 cases and the same number of controls. Population controls were randomly drawn from the mandatory registries of the reference communities (predefined communities in the vicinity of possible cases with comparable size and socioeconomic structure) and were individually matched for sex, age, and region of residence. All patients born in or after 1913 of German nationality with a diagnosis of lung cancer not older than 3 months at the date of interview were eligible. The response rate was 69 percent for cases and 68 percent for controls.

The other study was part of a then ongoing study on lung cancer risk and exposure to indoor radon in West and East Germany conducted by the GSF-National Research Center for Environment and Health, Neuherberg, from 1990 to 1996 (19). It covered the following regions: parts of Nordrhein-Westfalen, Rheinland-Pfalz and Bayern, the Saarland, Thüringen, and Sachsen. By 1994, 3,180 cases and 3,249 controls were enrolled. Cases were eligible if: 1) they were less than 76 years old; 2) they were resident in the study region; 3) they had lived in Germany for more than 25 years; and 4) diagnosis was not more than 3 months ago. The response rate among eligible cases was 77 percent. Population controls who satisfied inclusion criteria 1–3 were randomly selected from mandatory registries or by modified random digit dialing (20), and were frequency matched to cases on sex, age, and region. The response rate for controls was 41 percent.

In both studies, incident cases of lung cancer were included only if the diagnosis was cytologically and/or histologically ascertained and metastases secondary to other tumors had been excluded. Both cases and controls were interviewed face to face by trained interviewers with respect to their occupational exposure, residential history, smoking, and other risk factors. All subjects were interviewed in person, and no data were obtained from next of kin or other surrogates. Both studies employed the same occupational questionnaire, although the GSF Study, with its primary intention to study the impact of indoor radon on lung cancer risk, used a smaller subset of additional job-specific questionnaires.

Exposure assessment

A standardized questionnaire was applied to determine basic demographic characteristics in addition to details on smoking and a lifelong history of all jobs held for at least 6 months. Job titles and industries were coded according to the classification of the German Statistical Office (Statistisches Bundesamt, 1975 (21) and 1979 (22), 3-digits). All industries and job titles were grouped into 21 and 33 categories, respectively, as described before for the BIPS Study (18). Depending on their work histories, individuals contributed to multiple categories. Controls had worked on average in 2.7 different jobs among 2.6 different industries. By comparison, the cases had worked on average slightly more (2.9) different jobs in 2.8 different industries. Using "never exposed" workers as the reference category, risks were calculated for workers "ever exposed", i.e., worked for at least 6 months in one of 21 industries or held one of 33 job titles, respectively, as crude odds ratios (OR1), odds ratio adjusted for smoking (OR2), and odds ratio adjusted for smoking and asbestos exposure (OR3). While OR2 represents the typical risk estimate for an industry branch or job group, OR3 also takes into account the effect of asbestos exposure and, therefore, can be interpreted as a measure of risk in this industry or occupation independent of asbestos.

Occupational exposures of interest in this study were defined a priori for varying reasons: 1) being under consideration to be classified as an occupational carcinogen in Germany (silica, DEE, MMMF); 2) new definition of benzo[a]pyrene (BaP)-years instead of job requirements for compensation purposes (PAH); and 3) acting as a confounder in the context of our study (asbestos). Exposures were evaluated on the basis of job and industry codes and written job descriptions as well as on the basis of supplementary job-specific questionnaires. A subset of 20 out of 33 supplementary questionnaires applied by both the GSF Study and the BIPS Study (18) was used (see table 1). Cumulative exposure was assessed by expert rating according to job exposure matrices (silica and PAH), fully written description (DEE, MMMF) and semi-

TABLE 1. Supplementary questionnaires used in the pooled case-control study of occupational exposure and lung cancer, Germany, 1988–1996

Job-specific supplementary questionnaire
Roofer and installer of house tiling
Insulation installer
Ventilation and air conditioning technician, duct and pipe layer
Electrical and electronics fitters
Work in road construction and civil engineering
Stone mason, "terrazzo" layer
Metal production
Metalworking
Foundry
Heat protection
Welding, flame cutting
Automechanic
Mechanic, plumber, pipe fitter
Asbestos processing industries
Chemical and pharmaceutical industry, mineral oil processing, fertilizer production
Galvanizing, electroplating
Coking plant, gasworks
Mining
Shipbuilding, shipyards
Building construction (concrete worker, mason, plasterer)

automated quantification (asbestos) (23, 24). Duration of exposure was assessed as: >0–≤3, >3–≤10, >10–≤20, >20–≤30, and >30 years. The beginning and end of exposure was categorized as: first year of exposure (≤1945, 1946–1955, and ≥1956) and last year of exposure (≤1965, 1966–1975, and ≥1976).

Silica. With regard to silica exposure, two supplementary questionnaires were relevant: stone mason and "terrazzo" layer, and mining. The cumulative exposure E_{sil} was estimated for defined jobs within 13 risk industries according to:

$$E_{sil} = \sum_{i=1}^{n} p_i \times f_i \times c_i \times t_i[(\mathrm{mg/m^3})\mathrm{years}].$$

where n is the number of working periods for an individual subject. Weighting factors were given for probability p: 1 = certain, 0.3 = probable, 0.1 = possible; frequency of occupational exposure f: 1 = >50 percent, 0.3 = 10–50 percent, 0.1 = <10 percent in percent of working time; time t: duration of exposure in years; and concentration c: the respirable dust concentration was classified into four categories: low 0.01–0.07 mg/m^3 (0.04 mg/m^3), medium >0.07–0.15 mg/m^3 (0.11 mg/m^3), high >0.15–0.75 mg/m^3 (0.45 mg/m^3), and very high >0.75 mg/m^3 (1.0 mg/m^3). The mean dust concentration was taken for the job exposure matrix (JEM). The present German maximum working place concentration of fine respirable dust is 0.15 mg/m^3.

Polycyclic aromatic hydrocarbons (PAH). PAH-exposure was assessed by asking about the use of coal-tar pitch and bitumen in roofers and insulation installers; the kind of work in road construction workers; the use of coal-tar pitch, coal dust, and sawdust in foundry workers; and working on the top or side of a coke oven. The cumulative exposure E_{BaP} to benzo[a]pyrene as a marker of cumulative PAH-exposure was estimated for defined jobs within 10 risk industries according to:

$$E_{BaP} = \sum_{i=1}^{n} p_i \times f_i \times c_i \times t_i[(\mu\mathrm{g/m^3})\mathrm{years}].$$

where n is the number of working periods for an individual subject. Weighting factors were given for probability p: 1 = certain, 0.3 = probable, 0.1 = possible; frequency of occupational exposure f: 1 = >50 percent, 0.3 = 10–50 percent, 0.1 = <10 percent in percent of working time; time t: duration of exposure in years; and concentration c. Applying the measurements of benzo[a]pyrene at different working places by Lindstedt and Sollenberg (25), we classified the exposure as: low 0.1–2 μg/m^3 (1 μg/m^3), medium >2–10 μg/m^3 (6 μg/m^3), high >10–20 μg/m^3 (15 μg/m^3), and very high >20 μg/m^3 (30 μg/m^3).

Diesel engine exhaust (DEE). There was no specific questionnaire for DEE exposure. Working periods with DEE-exposure were identified by job code. Job codes with a potential for exposure to DDE were selected and divided into four groups: professional drivers of trucks, buses, taxis, etc.; other traffic-related jobs such as drivers of diesel locomotives and diesel forklift trucks; heavy equipment operators of bulldozers, graders, excavators; and full-time drivers of farming tractors. Because not all men, who had ever worked for at least 6 months in one of the above-mentioned jobs, were really exposed and to avoid misclassification, the written job description was evaluated and DEE-exposure ascertained without knowing the case/control status. Drivers of electrically driven locomotives or forklifts, for example, were not considered as exposed to DEE. Professional drivers were always included, even if they did not drive a diesel vehicle, assuming that DEE exposure was as much related to traffic conditions in general as to the driver's own vehicle. No attempt was made to estimate a cumulative exposure other than duration.

Man-made mineral fibers (MMMF). In the supplementary questionnaires, insulation installers and electrical and electronic fitters were asked whether they had installed or removed insulation and what kind of insulation material they had used.

Asbestos. Exposure was assessed on the basis of 17 job-specific supplementary questionnaires in a

semi-automated way (23, 24), yielding exposure measurements expressed as calendar years under exposure and duration in workdays. The effect of asbestos exposure was examined for its own sake but was also controlled for, which was important especially in the context of exposure to man-made mineral fibers, as it was strongly correlated with asbestos exposure.

Statistical analysis

Individually matched cases and controls of the BIPS Study and frequency matched cases and controls of the GSF Study were post-hoc stratified according to the matching variables age (6 categories) and region (17 categories). Odds ratios were calculated by conditional logistic regression (26) using the procedure PROC PHREG (27) or the program PECAN from EPICURE 2.0 (28). Subjects were defined as smokers if they had smoked regularly (at least one cigarette per day, 4 cigarillos/week, 3 cigars or 3 pipes/week) for at least 6 months at some time in life. Smoking exposure was explored in a series of phases, where a new phase was defined as a change in amount or type of tobacco product smoked. In each phase, information was available on the type of tobacco, amount smoked, duration in years, times of cessation, and year of starting. Smoking was included in all models by fitting pack-years as a continuous variable (log (pack-year + 1)), consumption of other tobacco products as a binary variable, and time since quitting smoking in four categories.

RESULTS

Demographic variables showed that cases were more often single, widowed, or divorced, and had a shorter education and a poorer vocational training than controls (see table 2). As expected, the proportion of lifelong nonsmokers was higher among controls than among cases. In the following text, results are summarized first by industry and occupation, then by specific exposures.

TABLE 2. Description of the study population: two case-control studies of occupational exposure and lung cancer, Germany, 1988–1996

	Controls		Cases	
	No.	%	No.	%
Pooled study (males)	3,541	100.0	3,498	100.0
West Germany	2,635	74.4	2,689	76.9
East Germany	906	25.6	809	23.1
Age (years), mean (SD*)	60.4 (8.6)		60.5 (8.5)	
Smoking status				
Lifelong nonsmoker	616	17.4	54	1.5
Current or ex-smoker	2,925	82.6	3,444	98.5
Marital status				
Single	102	2.9	141	4.0
Married or living together	3,174	89.6	3,001	85.8
Widowed	152	4.3	179	5.1
Divorced	112	3.2	171	4.9
Unknown	1	0.0	6	0.0
Education (years)				
<9	51	1.4	79	2.2
9–10	2,280	64.4	2,810	80.3
11–12	568	16.0	384	11.0
>12	638	18.0	215	6.1
Unknown	4	0.0	10	0.3
Vocational training				
None	352	9.9	697	19.9
Apprenticeship	1,783	50.4	2,162	61.8
Technical college	942	26.6	493	14.1
University	459	13.0	135	3.9
Unknown	5	0.0	11	0.0

* SD, standard deviation.

Industry and occupation

Lung cancer risk was evaluated for 21 industry and 33 job groups. A statistically significant increased odds ratio that could not be attributed to smoking or asbestos was seen for several industries (see table 3). Some of the industries have rather broad definitions. In the first category, agriculture, forestry, and fishing, an increased risk was seen for general farming (OR3 = 1.33, 95 percent CI 1.15, 1.53), horticulture (OR3 = 1.57, 95 percent CI 1.02, 2.40), and deep-sea fishing (OR3 = 4.41, 95 percent CI 1.36, 14.35), but not for forestry. In the category of energy and mining, the industries that contributed to the elevated risk were hard-coal mining, briquette production, and coke plants (OR3 = 1.42, 95 percent CI 1.12, 1.81). In the stone, glass, and pottery industries, an increased risk was especially found for quarrying (OR3 = 2.51, 95 percent CI 1.55, 4.07). For the paper, wood, and printing industries, the increased risk was restricted to the processing of wood (OR3 = 1.36, 95 percent CI 1.10, 1.67). Corresponding to the observed elevated risks in industries, several job groups showed an increased lung cancer risk (see table 4). Among agricultural workers, an increased risk was seen in general farm workers (OR3 = 1.30, 95 percent CI 1.11, 1.52), milkers (OR3 = 2.69, 95 percent CI 1.13, 6.43), and animal keepers (OR3 = 2.55, 95 percent CI 1.09, 5.97). In the group of service workers, the elevated odds ratio was restricted to cleaners (garbage disposal and vehicle and machinery cleaning (OR3 = 2.06, 95 percent CI 1.37, 3.11), while hotel and restaurant service workers and hair dressers had no increased risk. Most "white collar workers", e.g., architects, engineers and related technicians, sales workers, clerical workers, journalists, jurists, artists, medical and veterinary workers, teachers, scientists, and social workers, had a significantly decreased risk of lung cancer.

Crystalline silica

A total of 819 cases and 551 controls had ever worked for at least 6 months in a job with a silicosis risk, i.e., miners and foundry and quarry workers. Their risk was elevated (OR3 = 1.41, 95 percent CI 1.22, 1.62), increasing with the duration up to 30 years and decreasing thereafter (see table 5). The biggest

TABLE 3. Number of cases and controls according to industry code† and related risk‡ for men ever exposed in this industry: pooled case-control study of occupational exposure and lung cancer, Germany, 1988–1996

Industry	No. of controls	No. of cases	OR1	OR2	OR3	95% CI§
Agriculture, forestry, fishing	812	951	1.29*	1.30*	1.32*	1.05, 1.50
Energy and mining	274	440	1.72*	1.47*	1.44*	1.19, 1.74
Chemicals and oil	98	117	1.23	1.19	1.16	0.84, 1.62
Rubber and plastics	43	85	2.04*	1.94*	1.89*	1.23, 2.91
Stone, glass, and pottery	165	276	1.80*	1.55*	1.50*	1.19, 1.89
Metal production	574	764	1.45*	1.37*	1.27*	1.10, 1.46
Engine and vehicle building	791	1,000	1.40*	1.32*	1.21*	1.05, 1.38
Electrical and sheet metal	499	446	0.89	0.90	0.87	0.74, 1.02
Paper, wood, and printing	362	426	1.24*	1.28*	1.31*	1.10, 1.56
Leather and textile	183	182	1.03	1.02	1.04	0.81, 1.34
Food and tobacco	232	276	1.23*	1.04	1.07	0.86, 1.32
Construction	706	1,004	1.63*	1.35*	1.32*	1.15, 1.50
Installation	313	379	1.27*	1.14	1.08	0.90, 1.30
Wholesale and retail trade	475	404	0.83*	0.71*	0.73*	0.62, 0.87
Transportation	713	936	1.49*	1.24*	1.22*	1.07, 1.39
Shipping and storage	318	410	1.37*	1.13	1.14	0.95, 1.36
Financing and insurance	119	97	0.79	0.76	0.79	0.58, 1.10
Restaurants and hotels	128	166	1.36*	1.04	1.06	0.81, 1.39
Laundry, cleaning, personal hygiene, domestic services, garbage disposal	99	156	1.60*	1.24	1.27	0.95, 1.71
Education, health, research, and sports	1,663	1,065	0.50*	0.57*	0.59*	0.52, 0.66
Administration and welfare services	580	376	0.62*	0.56*	0.58*	0.49, 0.68

* $p < 0.05$, two-sided test.
† Source: Statistisches Bundesamt, 1979 (22).
‡ OR1, crude odds ratio; OR2, odds ratio, adjusted for smoking; OR3, odds ratio, adjusted for smoking and asbestos exposure.
§ 95% confidence interval for OR3.

TABLE 4. Number of cases and controls according to job group† and related risk‡ for men ever exposed in this job: pooled case-control study of occupational exposure and lung cancer, Germany, 1988–1996

Job group	No. of controls	No. of cases	OR1	OR2	OR3	95% CI§
Farmer, agricultural worker	662	770	1.26*	1.29*	1.31*	1.13, 1.51
Forestry worker, fisherman, livestock worker	125	179	1.52*	1.57*	1.61*	1.22, 2.11
Vegetable and orchard worker	94	118	1.27	1.28	1.31	0.95, 1.81
Farm manager, supervisor	47	23	0.51*	0.58	0.61	0.34, 1.10
Miner and quarryman	211	380	1.92*	1.64*	1.65*	1.34, 2.03
Stone cutter and carver	75	96	1.34	1.07	1.04	0.73, 1.47
Glass former and potter	42	71	1.76*	1.50	1.46	0.94, 2.28
Chemical processor	104	170	1.69*	1.56*	1.55*	1.15, 2.08
Paper maker, printer	76	71	0.95	0.87	0.89	0.61, 1.29
Cabinet maker, wood processing worker	274	314	1.20*	1.32*	1.36*	1.11, 1.66
Metal producer and processor	460	731	1.77*	1.49*	1.42*	1.22, 1.65
Machinery mechanic and fitter, plumber, sheet and structural metal worker	904	983	1.14*	1.13*	0.99	0.87, 1.14
Electrician	286	246	0.87	0.87	0.82	0.67, 1.02
Assembler, unskilled metal worker	45	53	1.16	1.66*	1.56	0.96, 2.54
Textile and leather worker	157	180	1.20	1.13	1.17	0.90, 1.51
Food and beverage processor	218	281	1.35*	1.14	1.17	0.95, 1.45
Bricklayer and carpenter	330	498	1.65*	1.39*	1.33*	1.11, 1.58
Road construction worker, pipelayer	355	492	1.47*	1.25*	1.24*	1.04, 1.47
Plasterer, insulator, and upholsterer	108	152	1.43*	1.37*	1.34*	1.00, 1.80
Painter and lacquerer	96	147	1.60*	1.39*	1.42*	1.05, 1.92
Stock clerk	106	121	1.18	1.03	1.02	0.74, 1.38
Unskilled worker	57	88	1.60*	1.37	1.36	0.91, 2.03
Stationary engine and heavy equipment operator	127	274	2.35*	1.86*	1.78*	1.39, 2.29
Architect, technician, engineer	754	409	0.49*	0.61*	0.60*	0.52, 0.70
Sales worker	565	447	0.76*	0.70*	0.73*	0.62, 0.85
Transport worker and freight handler	878	1,203	1.64*	1.30*	1.28*	1.13, 1.45
Administrative and clerical worker	1,056	688	0.58*	0.62*	0.65*	0.57, 0.74
Protective service worker	608	590	1.01	0.85*	0.85*	0.73, 0.99
Journalist, jurist, artist	144	79	0.55*	0.44*	0.47*	0.34, 0.64
Medical, dental, and veterinary worker	83	43	0.50*	0.58*	0.60*	0.39, 0.93
Social worker, teacher, and scientist	361	122	0.32*	0.39*	0.41*	0.32, 0.52
Service worker: hairdresser, hotel and restaurant service, laundry and dry cleaner, cleaner (building, road, vehicles, machinery)	141	227	1.69*	1.38*	1.39*	1.09, 1.79
Trainees, or jobs not elsewhere classified	75	89	1.21	1.06	1.07	0.74, 1.53

* $p < 0.05$, two-sided test.
† Source: Statistisches Bundesamt, 1979 (21).
‡ OR1, crude odds ratio; OR2, odds ratio, adjusted for smoking; OR3, odds ratio, adjusted for smoking and asbestos exposure.
§ 95% confidence interval for OR3.

group of workers with silicosis risk had worked as coalminers. After >20 years of exposure, the odds ratio of coalminers, adjusted for smoking and asbestos exposure, was 2.77 (95 percent CI 1.34, 5.74). Cumulative exposure to silica could be estimated according to the job exposure matrix in 513 cases and 321 controls. There was a significant trend ($p < 0.03$) between silica exposure and lung cancer risk. We found an OR3 of 1.91 (95 percent CI 1.39, 2.63) after a cumulative crystalline silica exposure of more than 5 mg/m^3 × years.

Polycyclic aromatic hydrocarbons (PAH)

A total of 181 cases and 94 controls were exposed to PAH. The evaluation of lung cancer risk showed a

TABLE 5. Lung cancer risk† in men ever exposed to crystalline silica, diesel engine exhaust (DEE), man-made mineral fibers (MMMF), or polycyclic aromatic hydrocarbons (PAH) by duration and cumulative exposure: pooled case-control study of occupational exposure and lung cancer, Germany, 1988–1996

Exposure	No. of controls	No. of cases	OR1	OR2	OR3	95% CI‡
Crystalline silica						
Never exposed	2,990	2,679	1.00§	1.00§	1.00§	
Ever exposed	551	819	1.67*	1.44*	1.41*	1.22, 1.62
Calendar years exposed						
>0–3	207	272	1.47*	1.36*	1.34*	1.08, 1.68
>3–10	154	220	1.62*	1.37*	1.33*	1.04, 1.70
>10–20	77	126	1.87*	1.49*	1.45*	1.04, 2.02
>20–30	45	100	2.42*	2.34*	2.28*	1.50, 3.47
>30	68	101	1.66*	1.22	1.21	0.84, 1.73
Cumulative exposure (mg/m³) to silica according to JEM¶						
>0–1	126	168	1.42*	1.29	1.21	0.92, 1.60
>1–5	115	179	1.71*	1.44*	1.39*	1.05, 1.84
>5	80	166	2.28*	1.90*	1.91*	1.39, 2.63
DEE						
Never exposed	3,111	2,782	1.00§	1.00§	1.00§	
Ever exposed	430	716	1.91*	1.46*	1.43*	1.23, 1.67
Calendar years exposed						
>0–3	102	132	1.48*	1.31	1.28	0.95, 1.73
>3–10	115	155	1.54*	1.26	1.21	0.91, 1.61
>10–20	75	165	2.54*	1.91*	1.84*	1.34, 2.52
>20–30	74	148	2.34*	1.63*	1.62*	1.16, 2.24
>30	64	116	2.07*	1.34	1.35	0.95, 1.93
MMMF						
Never exposed	3,371	3,194	1.00§	1.00§	1.00§	
Ever exposed	170	304	1.92*	1.71*	1.48*	1.17, 1.88
Calendar years exposed						
>0–3	29	51	1.83*	1.87*	1.68	0.98, 2.88
>3–10	38	69	1.91*	1.55	1.38	0.86, 2.20
>10–20	55	76	1.51*	1.36	1.17	0.77, 1.77
>20–30	30	61	2.23*	2.03*	1.69*	1.01, 2.81
>30	18	47	2.79*	2.39*	2.03*	1.04, 3.95
PAH						
Never exposed	3,447	3,317	1.00	1.00	1.00§	
Ever exposed	94	181	1.97*	1.66*	1.53*	1.14, 2.04
Calendar years exposed						
>0–3	33	40	1.24	1.20	1.16	0.68, 1.98
>3–10	22	58	2.79*	2.19*	2.02*	1.17, 3.48
>10–20	13	36	2.77*	2.16*	2.03	0.96, 4.31
>20–30	13	23	1.82	1.59	1.40	0.65, 3.01
>30	13	24	1.82	1.34	1.16	0.54, 2.52
Cumulative exposure to PAH according to JEM						
>0–20 BaP-years	56	80	1.49*	1.26	1.15	0.77, 1.71
>20 BaP-years	38	101	2.69*	2.26*	2.09*	1.36, 3.22

* $p < 0.05$, two-sided test.

† OR1, crude odds ratio; OR2, odds ratio, adjusted for smoking; OR3, odds ratio, adjusted for smoking and asbestos exposure.

‡ 95% confidence interval for OR3.

§ Reference category.

¶ JEM, job exposure matrix. Note: not all workers ever exposed to silica could be classified according to JEM.

crude odds ratio (OR1) of 1.97 (see table 5) that decreased after adjustment for smoking and asbestos exposure (OR3 = 1.53, 95 percent CI 1.14, 2.04). The odds ratio was only slightly increased in low/short time exposed workers (>0–20 BaP-years) (OR3 = 1.15, 95 percent CI 0.77, 1.71), whereas it was markedly increased in highly/long time exposed (>20 BaP-years) workers (OR3 = 2.09, 95 percent CI 1.36, 3.22). There is no linear relation between exposure in BaP-years and the risk of lung cancer. However, after log-transformation, a significant increase in risk according to the level of exposure can be shown (β = 0.132 (95 percent CI 0.044, 0.219)). As expected, the risk was highest for workers of coking plants and less so in smelters and furnacemen. No increased risk was seen for foundry workers and chimney sweeps after adjustment for smoking and exposure to asbestos.

Diesel engine exhaust (DEE)

The evaluation of lung cancer risk for all jobs with DEE-exposure (716 cases, 430 controls) combined showed a crude odds ratio (OR1) of 1.91 that decreased after adjustment for smoking and asbestos exposure (OR3 = 1.43, 95 percent CI 1.23, 1.67) (see table 5). Although the risk seems to increase with duration of exposure to DEE up to the category 10–20 years exposed, later on it levels off. The risk was increased in nearly all job categories analyzed with the effect being strongest for most recent exposure, i.e., beginning after 1955 and ending after 1975. The largest group (534 cases, 337 controls) of men with DEE exposure, the professional drivers (e.g., truckdriver, busdriver, taxidriver, etc.), showed an increased odds ratio (OR3 = 1.25, 95 percent CI 1.05, 1.47). DEE exposure in other traffic-related jobs (e.g., diesel engine locomotive drivers, switchmen, forklift operators) was also associated with an elevated odds ratio (OR3 = 1.53, 95 percent CI 1.04, 2.24). Heavy equipment operators showed the highest risk (OR3 = 2.31, 95 percent CI 1.44, 3.70). The risk of tractor drivers—although overall not significantly elevated—increased with length of employment and reached statistical significance for exposures longer than 30 years (OR3 = 6.81, 95 percent CI 1.17, 39.51).

Man-made mineral fibers (MMMF)

A total of 304 cases and 170 controls were ever exposed to MMMF. The odds ratio adjusted for smoking and asbestos exposure (OR3) was 1.48 (95 percent CI 1.17, 1.88) (see table 5). We calculated a more than twofold risk (OR3 = 2.03, 95 percent CI 1.04, 3.95) for exposures of more than 30 years. To be sure to exclude any confounding effect of asbestos, we identified those cases and controls who insulated with glass wool or mineral wool mats only, but never reported any asbestos exposure in the supplemental questionnaires. This restriction holds for 51 cases and 28 controls. When adjustment was made for smoking, an elevated risk was found in this group (OR2 = 1.56, 95 percent CI 0.92, 2.65).

Asbestos

Ever exposure to asbestos was associated with a crude odds ratio (OR1) of 1.58 which was reduced after adjustment for smoking (OR2 = 1.41, 95 percent CI 1.24, 1.60) (see table 6). A clear gradient was seen for both calendar years under exposure and duration in days with a smoking-adjusted odds ratio (OR2) of 1.79 (95 percent CI 1.39, 2.30) for more than 2,500 exposed workdays.

DISCUSSION

The present study revealed evidence of an increased lung cancer risk associated with particular industries and occupations. Such associations have been described in part before (29).

Agriculture, forestry, and fishing

According to the International Agency for Research on Cancer (IARC) (29), lung cancer risk in this group is confined to vineyard workers using arsenic insecticides. In our study, winegrowers made up only a very small subgroup (n = 21) of agricultural workers included in the study, and they showed no increased risk. Arsenic-containing insecticides were banned in Germany shortly after World War II. Exposure to pesticides in general (30, 31) has also been described to be associated with an increased lung cancer risk. Unfortunately, the supplementary questionnaire covering specific exposures in agriculture—although included in the BIPS Study—was not used in the GSF Study so that no data on specific exposures in agriculture from that study could be evaluated. A striking finding was that persons in agricultural occupations who had contact with animals, such as milkers and animal keepers, showed a significantly elevated odds ratio. Previous studies of farmers (32, 33) have demonstrated excess cancer risk, but mainly for tumors of the hematopoietic and lymphatic systems. Excess of lung cancer in relation to animal contact has consistently been reported only in the meat industry (34–36).

Energy and mining

As expected, workers in coke plants and gasworks had an increased lung cancer risk, most likely due to

TABLE 6. Lung cancer risk† in workers ever exposed to asbestos: pooled case-control study of occupational exposure and lung cancer, Germany, 1988–1996

Exposure	No. of controls	No. of cases	OR1	OR2	95% CI‡
Total					
Never exposed	2,736	2,408	1.00§	1.00§	
Ever exposed	805	1,090	1.58*	1.41*	1.24, 1.60
Calendar years exposed					
>0–3	80	95	1.39*	1.22	0.85, 1.74
>3–10	261	297	1.31*	1.19	0.96, 1.46
>10–20	186	283	1.77*	1.45*	1.16, 1.82
>20–30	137	193	1.63*	1.45*	1.12, 1.88
>30	141	222	1.86*	1.86*	1.43, 2.42
Days exposed					
<50	83	83	1.15	1.30	0.89, 1.88
50–250	191	225	1.38*	1.27*	1.00, 1.60
251–2,500	394	543	1.61*	1.36*	1.15, 1.61
>2,500	137	239	2.02*	1.79*	1.39, 2.30
First year of exposure					
≤1945	149	181	1.32*	1.21	0.92, 1.58
1946–1955	320	397	1.46*	1.44*	1.19, 1.74
≥1956	336	512	1.82*	1.47*	1.23, 1.76
Last year of exposure					
≤1965	302	321	1.20*	1.16	0.95, 1.41
1966–1975	170	212	1.47*	1.17	0.92, 1.49
≥1976	333	557	1.98*	1.76*	1.48, 2.10

* $p < 0.05$, two-sided test.
† OR1, crude odds ratio; OR2, odds ratio, adjusted for smoking.
‡ 95% confidence interval for OR2.
§ Reference category.

exposure to benzo[a]pyrene and coal carbonization products, which are well-known for their carcinogenic potential. We found an elevated risk in mineral-coal mining, which may be related to the exposure of crystalline silica dust (37–39). As former employment at the uranium mining company "Wismut" was an exclusion criterion in the indoor radon study of GSF, the very few study subjects with occupational exposure to radon decay products came from the BIPS Study.

Chemical and oil industries

Lung cancer in the chemical industry is related to the exposure of bis(chloromethyl)ether and chloromethylether as well as pigment chromate production. Data from our supplementary questionnaires revealed few such exposures. No increased lung cancer risk was observed for the chemical industry.

Rubber industry

The production of rubber is regarded as a carcinogenic risk by the IARC. Solvent naphtha and aromatic amines are used in rubber and synthetic latex manufacture, calendering, and tire curing and represent a risk factor for leukemia and bladder cancer. The evidence of an increased lung cancer risk in our study corroborates earlier results of a cohort study (40) among 11,663 workers in the German rubber industry, which found increased mortality rates from lung cancer and mesothelioma, most likely due to the exposure to talcum contaminated by asbestos.

Stone, glass, and pottery industries

These industries are well known for their increased risk of silicosis, and in contrast to mining crystalline silica, is the only suspected lung carcinogen in this industry. No confounding by additional exposure to arsenic, radon, diesel engine emissions, or asbestos has to be presumed. The increased lung cancer risk that we observed in these industries adds evidence to the IARC evaluation (37) that crystalline silica inhaled in the form of quartz or cristobalite from occupational sources is carcinogenic to humans.

Metal production industry

Several jobs in the metal production industry have been associated with an increased risk of lung cancer: aluminum production (PAH), copper smelting (arsenic), chromate production (chromium-VI-compounds), chromium plating (chromium-VI-compounds), iron and steel founding (not identified), nickel refining (nickel compounds), pickling operations (inorganic acid mists containing sulfuric acids), cadmium production and refining (cadmium and cadmium compounds), and beryllium refining (beryllium and beryllium compounds). Only a few subjects in our study could be allocated to specific exposures and no evaluation was attempted. We found an increased lung cancer risk especially in the heat-treatment and refinement of steel and the production of steel and light-metal constructions.

Engine and vehicle building

The increased lung cancer risk of shipyard and dockyard workers as well as motor vehicle and railroad manufacture workers according to IARC (29) is due to asbestos exposure. In our study, lung cancer risk decreased remarkably after adjusting for asbestos exposure. It remained of borderline statistical significance, though, which may indicate an actual weak effect or be due to residual confounding.

Wood industries

In 1995, IARC (41) classified wood dust as a human carcinogen, based on very strong evidence of a carcinogenic risk of sino-nasal cancer. An excess of lung cancer among persons employed in wood industries has been reported before. In the American Cancer Society's Cancer Prevention Study-II, Stellman et al. (42) investigated the mortality experience of 362,823 men enrolled in 1982 and followed up for 6 years. Within this group, 45,399 men (12.5 percent) reported either employment in a wood-related occupation or exposure to wood dust, or both. Among men who reported exposure to wood dust, there was an elevated risk of lung cancer (relative risk (RR) = 1.17, 95 percent CI 1.04, 1.31).

Construction industry

In the construction industry, we found an increased lung cancer risk in insulators and pipe coverers, who were exposed to asbestos, and in roofers and asphalt workers exposed to PAH, as has been described by the IARC (29). Lung cancer risk was also increased in insulators, who had not been exposed to asbestos but only to man-made mineral fibers. The carcinogenic potential of man-made mineral fibers has been shown in various animal experiments, but evidence of carcinogenicity in humans is limited (43).

Exposure to crystalline silica

The relation between exposure to crystalline silica and lung cancer has been a controversial topic, and findings have appeared inconsistent. In a meta-analysis of 23 studies, Smith et al. (44) found a twofold risk (RR = 2.2, 95 percent CI 2.1, 2.4). The authors concluded that the association between silicosis and lung cancer was causal, either due to silicosis itself, or due to a direct effect of the underlying exposure to silica. Our study showed a positive correlation between the height of exposure, measured by the job exposure matrix, and the lung cancer risk. At present, in Germany, lung cancer in silicotic patients is only considered a occupational disease making the patient eligible for compensation if the tumor arises from cicatrice tissue.

Exposure to PAH

Since 1988, cancer of the lung caused by coke oven emissions has been recognized as an occupational disease in Germany. Our study showed that the elevated lung cancer risk was not restricted to coke oven workers, but was also observed in other jobs with an exposure to PAH, such as road construction workers, pavers, roofers, and insulators, and persons who worked with coal tar pitch, bitumen, and/or asphalt. The German government now requires that this occupational cancer is defined by a minimum exposure to benzo[a]pyrene instead of as in the past the naming one job with an extremely high exposure.

Exposure to DEE

In 1989, the IARC (45) concluded that there was sufficient evidence for the carcinogenicity of whole diesel exhaust in experimental animals, but considered the evidence in humans as limited. Although most epidemiologic studies show an association between exposure to DEE and lung cancer risk, uncertainty remains, because the observed effects are rather small, making them prone to confounding error. In addition, the lack of quantitative information on historic exposure to diesel motor emissions precludes the evaluation of a dose-response relation. In 21 of 23 published cohort and case-control studies that met inclusion criteria for a meta-analysis, Bhatia et al. (46) observed relative risk estimates greater than one for lung cancer (pooled RR = 1.33, 95 percent CI 1.24, 1.44).

Study weaknesses and strengths

A weakness of the present study lies in the limited exposure assessment available. As in most other case-control studies, many exposures could only be defined as work in an occupation. Nondifferential misclassification is a very likely source of bias under these circumstances, leading to an odds ratio that is biased toward one and an underestimation of the true risk of lung cancer.

The population investigated in our study was heterogeneous, with some regions being more industrialized, others more rural, and with diverse political systems in the past. Because we matched for region, this makes confounding by environmental or other region-specific risk factors an unlikely explanation for the observed associations.

To investigate whether the low response among controls in the GSF Study has influenced the results, a nonresponse analysis was conducted in a subsample of refusals. Nonresponse was mainly due to refusals of long-term (1 year) measurements of radon required in the subject homes (38 percent), no time for interview and organization of measurement (13 percent) followed by illness (13 percent) and other reasons. People from the lower social class were underrepresented among GSF controls compared with the BIPS Study. Because there is a strong correlation between social status and exposure to occupational risk factors, we evaluated the effect of adjusting for social status in three categories (1, without any formal vocational training; 2, finished vocational training; 3, university degree) on the risk estimates for the exposure to crystalline silica, DEE, and PAH. Inclusion of social status as a covariable in the model shifted the odds ratios found for the above-mentioned occupational exposures by 5–15 percent toward one, but they remained statistically significant for PAH and DEE (silica, OR3 from 1.91 to 1.70; PAH, OR3 from 2.08 to 1.82; and DEE, OR3 from 1.43 to 1.26). On the other hand, it has to be discussed that adjustment for socioeconomic status may lead to overadjustment and thus artificially reduces the risk of occupational hazards.

The joint evaluation of two case-control studies on lung cancer offered the advantage of a big study size entailing high statistical power. Another strength lies in the detailed lifelong description of all occupations and industries in which a study subject was ever employed and the extensive smoking history available. Special attention was given to smoking as a confounder by testing several models. When we combined the variables pack-years, type of tobacco product, and years since quitting smoking, we achieved a very good fit. A residual bias due to smoking cannot be excluded, but it was minimized. In addition, we controlled adequately for the confounding effect of asbestos exposure.

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