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Lung Cancer Risk in Hard-Metal Workers

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An industry-wide mortality study on the association between lung cancer and occupational exposure to cobalt and tungsten carbide was carried out in the French hard-metal industry. This case-control study was nested in the historical cohort of workers ever employed in this industry's 10 facilities, most of which are located in eastern France. Workers were followed up from 1968 to 1991. Occupational exposure was assessed using a job-exposure matrix that provided semiquantitative scores for 320 job periods. These scores were significantly correlated with the levels of cobalt measured in 744 historical air samples. In this cohort, which comprised 5,777 males and 1,682 females, the death rate from lung cancer was significant (63 deaths, standardized mortality ratio = 1.30, 95% confidence interval (CI) 1.00–1.66) when compared with national death rates. Sixty-one cases and 180 controls were included in the study. When the exposures during the last 10 years were ignored, a twofold lung cancer risk was observed among workers simultaneously exposed to cobalt and tungsten carbide (odds ratio (OR) = 1.93, 95% CI 1.03–3.62) adjusted for other cobalt exposure (OR = 2.21, 95% CI 0.99–4.90). The odds ratios increased with cumulative exposure (first quartile, OR = 1.00; second quartile, OR = 2.64; third quartile, OR = 2.59; fourth quartile, OR = 4.13) and, to a lesser degree, with duration of exposure (one decade, OR = 1.00; two decades, OR =1.61; three decades, OR = 2.77; four decades, OR = 2.03). Adjustments for smoking and for exposures to known or suspected carcinogens did not change the results, yet the odds ratio for smoking (3.38) was lower than expected, suggesting the possibility of some misclassification. Occupational risk was highest among smokers. This study supports the hypothesis that workers who manufacture hard metals have an increased mortality from lung cancer due to simultaneous exposure to cobalt and tungsten carbide. *Am J Epidemiol* 1998;148:241–8.

case-control studies; cobalt; cohort studies; lung neoplasms; tungsten compounds

In a 1991 monograph, the International Agency for Research on Cancer (1) concluded that cobalt and cobalt compounds are possibly carcinogenic to humans. The sole evidence for this conclusion consists of the few epidemiologic studies investigating the risk of lung cancer among workers exposed to cobalt. For example, the incidence of lung cancer mortality was significantly increased among workers employed in the cobalt production workshop of a French electrochemical factory (2), although this finding was not confirmed in the cohort update (3). Cobalt exposure is associated with tungsten carbide exposure in the hard-metal manufacturing industry, because the process involves sintering a mixture of cobalt powder (as much as 20 percent) and tungsten carbide powder. An increased mortality from lung cancer was observed among the workers of three Swedish factories (4) and one French factory (5). The present study was designed to clarify whether a possible lung cancer risk exists in this industry. More specifically, it was aimed at assessing workers' risk of lung cancer in relation to simultaneous occupational exposure to cobalt and tungsten carbide when producing hard metals.

This paper reports the findings of this multicentric mortality study involving all French factories that produce hard metals. The case-control study was nested in the historical cohort of all workers ever employed in this industry.

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Abbreviations: CI, confidence interval; OR, odds ratio; SMR, standardized mortality ratio.

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MATERIALS AND METHODS

Exposure assessment

In addition to hard-metal manufacture, other production activities had been performed in some of the factories studied. Powder metallurgy processes were used to produce equipment made of single, pure metals (iron or nickel) or of alloys containing iron, copper, and tin; foundry processes were performed to produce cobalt superalloys and magnets made of cobalt, tungsten, nickel, chromium, and carbon.

A committee of nine experts comprising epidemiologists, occupational physicians, industrial hygienists, and industry representatives was set up to develop a job-exposure matrix. The matrix contained 320 job periods and assigned semiquantitative estimates of exposure to cobalt and to tungsten carbide, that is, an intensity score of 0 (no exposure) to 9 (highest exposure level) and a frequency score of <10 percent, 10–50 percent, and >50 percent of the working time. In addition, nine potential carcinogens (6) were considered: polycyclic aromatic hydrocarbons, asbestos, silica, certain chromium compounds, certain nickel compounds, arsenic compounds, cadmium compounds, nitrosamines, and benzene. The job-exposure matrix was developed by a consensus of experts using a delphi method (for details, refer to Moulin et al. (7)).

In addition to use of the job-exposure matrix, 744 atmospheric concentrations of cobalt previously measured in the factories studied (8–10) were considered to enable matrix scores to be validated. All of these cobalt measurements were obtained by the same laboratory, using plasma emission spectrometry. A correlation between the job-exposure matrix and the cobalt measurements was established by regressing the matched cobalt-intensity scores from the matrix with the log-transformed measurements. It is noteworthy that the experts were unaware that these measurements existed before developing the job-exposure matrix.

Cohort study

The cohort comprised all male and female workers ever employed for at least 3 months in any of the 10 French factories of the hard-metal industry, from the time each factory opened until December 31, 1991. The mortality follow-up period was January 1, 1968 (or from the first date of employment, if later) to December 31, 1991. Because personnel records were incomplete for factories 2, 6, and 8, the cohorts there were defined as all workers present on a certain date (1950, 1975, and 1980, respectively) and those hired later. The minimum duration of employment was 1 year in factory 4, the previously studied cohort (5) that was updated in this study. Vital statistics on subjects were gathered from the registry offices in their birthplaces and by checking a file of all subjects who died in France. The causes of the 684 registered deaths were ascertained from death certificates (633 subjects) and from medical records (29 subjects). The cause of death was unknown for 22 subjects (3.2 percent).

Using the computer program written by Coleman et al. (11) and standard methods described by Breslow and Day (12), we computed the number of person-years at risk, the expected number of causes of death, and the standardized mortality ratios on the basis of national death rates. The 95 percent confidence intervals of the standardized mortality ratios were computed under the standard Poisson assumption (12). Because of a lack of reliable information on the vital status of all workers born abroad, they were considered lost to follow-up and were censored on the date they left the factory.

Case-control study

The cases were the cohort workers who had died of lung cancer. Three controls per case were sampled from the set of those at risk, that is, from all subjects 1) under follow-up on the date that the case died, having completed 3 months of employment and known to be alive on that date, and 2) of the same sex and with the same date of birth ±6 months. The main sources of information on the job histories of cases and controls were administrative records (71.6 and 65.0 percent, respectively) and interviews with colleagues (18.9 and 26.3 percent, respectively). Most of the information on the smoking habits (defined as never, former, or current smokers) of cases and controls was obtained by interviewing colleagues (70.5 and 51.3 percent, respectively), relatives (11.5 and 9.1 percent, respectively), and the subjects themselves (0 and 18.8 percent, respectively). This information was summarized as ever versus never smoker, as no time scale was available.

Multiple conditional logistic regression analysis was used to estimate both the odds ratios and the 95 percent confidence intervals (13), obtained after ignoring the exposures during the last 10 years. Occupational exposure of cases and controls was then obtained by matching job periods from the job-exposure matrix with job histories. The qualitative definition of cobalt exposure was 1) simultaneous exposure to cobalt and tungsten carbide specific to hard-metal manufacture and 2) other cobalt exposure resulting from other production activities.

Cobalt exposure was analyzed using the maximum intensity score coded over the job history, the duration of exposure at an intensity of ≥2, and the estimated cumulative exposure. Cumulative exposure was ex-

pressed as either an unweighted (intensity × duration) or a frequency-weighted (intensity × duration × frequency) score. The cumulative exposure scores were divided into four contiguous categories according to quartiles of the exposure distribution among controls, so that each category contained 25 percent of the controls. Duration was divided into nonexposed, <10, 10–20, and >20 years of exposure. The fit of the ranks of these recoded variables was used as a test for trend.

The effect of possible confounders, such as potential carcinogens (6) listed on the job-exposure matrix, employment in a maintenance workshop, socioeconomic level (staff vs. nonstaff) (14), and smoking, was assessed using a multiple logistic model. In addition, a possible interaction between smoking and exposure was tested by fitting the exposure among smokers into a model containing the main effects of smoking and exposure.

Quality assurance

The epidemiology department of the Institut National de Recherche et de Sécurité has developed a quality assurance system based on Chemical Manufacturers Association (15) recommendations for good epidemiology practices in occupational epidemiologic research. In 1995, the French Association for Quality Assurance certified that this system conforms to the requirements of International Standards Organization standard 9002 (16).

RESULTS

Exposure assessment

Measurements of atmospheric cobalt concentrations were obtained from 382 short-duration (15–20 minutes) area samples with a high flow rate (50–150 liters/minute), which were gathered between 1971 and 1983, and from 362 more recent (1982–1994) long-duration (4–8 hours) samples with a lower flow rate (1–2 liters/minute), 264 of which were personal samples. In hard-metal production areas, excluding the cobalt powder manufacturing workshop, a linear regression between the cobalt levels that the experts assigned in the job-exposure matrix and the log-transformed measurements showed significantly increasing trends in the short-duration area samples ($p < 0.0001$), long-duration area samples ($p = 0.015$), and long-duration personal samples ($p = 0.015$). Table 1 shows the cobalt measurements obtained from the personal samples.

Cohort study

The information in table 2 describes the study population. The mean length of follow-up was 15.4 years. A total of 1,131 workers was considered lost to follow-up, 875 of whom were born abroad.

The overall observed mortality for both sexes was lower than expected (standardized mortality ratio (SMR) = 0.93), reaching statistical significance for males. Elevated standardized mortality ratios were observed for lung cancer in males (SMR = 1.29), reaching borderline statistical significance in the total population (63 deaths, SMR = 1.30, 95 percent confidence interval (CI) 1.00–1.66) (table 3). No trend was observed when considering lung cancer mortality by year of hire, age at death, year of death, or duration of employment. However, lung cancer risk increased slightly with time since first employment (0–9 years, SMR = 0.74 (3 deaths observed); 10–19 years, SMR = 1.33 (17 deaths observed); 20–29 years, SMR = 1.42 (25 deaths observed); >30 years, SMR = 1.25 (16 deaths observed)) (data not shown). The observed mortality from diseases of the cardio-

TABLE 1. Correlation between measured cobalt concentrations* in workshops† and levels assigned in the job-exposure matrix, French cohort of hard-metal workers, 1968–1991

Job-exposure levels	No. of samples	Arithmetic means (μg/m³)	Minimum (μg/m³)	Maximum (μg/m³)	Geometric means (μg/m³)	Geometric SD‡	Ratio of 97.5 to 2.5 percentiles§
1	0						
2	70	39.37	1	228	20.04	3.30	108
3	59	63.38	0.5	449	18.25	5.41	748
4	98	62.33	2	465	26.41	3.67	163
5	32	87.91	1	515	28.59	6.11	1,206
6	2	169.00	134	204	165.34	1.35	3.24
7	3	102.33	34	155	85.36	2.25	24.0
>7	0						
Total	264						

* Individual time-weighted-average samples.
† Cobalt powder manufacturing excluded.
‡ SD, standard deviation.
§ Assuming a log-normal distribution of measured cobalt concentrations.

TABLE 2. Description of the study population, French cohort of hard-metal workers, 1968–1991

Factories	Year opened	No. of subjects			Person-years		
		Men	Women	Total	Men	Women	Total
1	1945	2,328	667	2,995	41,479	11,908	53,387
2	1942	596	324	920	8,581	4,772	13,353
3	1959	590	229	819	9,876	4,082	13,958
4	1956	711	63	774	11,452	1,010	12,462
5	1970	428	153	581	4,310	1,541	5,851
6	1948	468	48	516	6,395	594	6,989
7	1965	270	72	342	3,027	875	3,902
8	1972	233	72	305	2,105	724	2,829
9	1947	136	51	187	1,298	527	1,825
10	1965	51	8	59	569	94	663
Total*		5,777	1,682	7,459	88,738	26,096	114,834

* Total includes 39 workers employed in two factories and contributing to 385 person-years.

TABLE 3. Standardized mortality ratios (SMRs) and 95% confidence intervals (CIs) for selected causes of death among 7,459 subjects (5,777 men), French cohort of hard-metal workers, 1968–1991

Causes of death	ICD-8 codes*	Men				Both sexes			
		Observed	Expected†	SMR	95% CI	Observed	Expected†	SMR	95% CI
All causes	1–999	591	644.59	0.92	0.84–0.99	684	732.57	0.93	0.87–1.01
Circulatory system									
All circulatory diseases	390–459	139	158.30	0.88	0.74–1.04	160	181.12	0.88	0.75–1.03
Ischemic heart diseases	410–414	56	62.12	0.90	0.68–1.17	63	67.80	0.93	0.71–1.19
Respiratory system									
All respiratory diseases	460–519	22	29.21	0.75	0.47–1.14	24	32.61	0.74	0.47–1.09
Chronic bronchitis, emphysema	490–492	1	4.69	0.21	0.00–1.19	2	5.02	0.40	0.05–1.44
Pneumoconiosis	515–516	3	2.25	1.33	0.27–3.89	3	2.26	1.33	0.27–3.87
Fibrosis	517	0	0.62	0.00	0.00–5.95	0	0.71	0.00	0.00–5.22
Malignant neoplasms									
All cancer sites	140–208	209	203.06	1.03	0.89–1.18	247	231.91	1.07	0.94–1.21
Buccal cavity, pharynx	140–149	23	19.51	1.18	0.75–1.77	24	19.92	1.20	0.77–1.79
Larynx	161	7	12.80	0.55	0.22–1.13	7	12.93	0.54	0.22–1.12
Esophagus	150	19	15.30	1.24	0.75–1.94	19	15.61	1.22	0.73–1.90
Lung	162	61	47.22	1.29	0.99–1.66	63	48.59	1.30	1.00–1.66
Pleura	163	3	1.39	2.16	0.45–6.31	3	1.51	1.98	0.41–5.79
Bladder	188	4	5.43	0.74	0.20–1.88	5	5.74	0.87	0.28–2.03

* World Health Organization. International classification of diseases. Manual of the international statistical classification of diseases, injuries, and causes of death. Eighth Revision. Geneva, Switzerland: World Health Organization, 1968.
† Expected numbers using national death rates, after adjustment for sex, age, and calendar time, censored at age 85 years.

vascular system and diseases of the respiratory system was slightly lower than expected. A nonsignificant excess for both sexes (SMR = 1.98) was observed for pleural tumors.

Case-control study

Job histories could not be obtained for two cases and four controls; therefore, 61 cases and 180 controls were finally eligible for the case-control study. Table 4 summarizes some characteristics of the study sample. Information on smoking habits was available for 80 percent of the study population.

The odds ratio contrasting simultaneous cobalt and tungsten carbide exposure rated as greater than an intensity score of 2 with nonexposed work was significantly greater than 1.00, after adjusting for all other cobalt exposures (table 5). Significant increasing trends were observed with duration of exposure and with unweighted cumulative exposure. The odds ratios for other cobalt exposures ranged from 1.83 to 2.21.

Exposure to cobalt and tungsten carbide before and after sintering was considered simultaneously in a multiple regression analysis. Before-sintering exposure was associated with an elevated risk (odds ratio (OR) = 1.69, 95 percent CI 0.88–3.27), which increased significantly with frequency-weighted cumulative exposure (p = 0.03). The odds ratio for after-sintering

TABLE 4. Description of 61 cases and 180 controls, French cohort of hard-metal workers, 1968–1991

	Cases	%	Controls	%
Sex				
Male	59	96.7	174	96.7
Female	2	3.3	6	3.3
Smoking habits				
Never	12	19.7	65	36.1
Former	9	14.8	34	18.9
Current	24	39.3	42	23.3
Former or current	5	8.2	2	1.1
Unknown	11	18.0	37	20.6
Year of hire				
≤1949	3	4.9	9	5.0
1950–1959	29	47.5	82	45.6
1960–1969	25	41.0	62	34.4
1970–1979	4	6.6	23	12.8
≥1980	0	0.0	4	2.2
Year of birth				
Median	1924		1924	
Range	1900–1951		1899–1951	
Year of death				
Median	1984			
Range	1968–1991			
Age at death (years)				
Median	60			
Range	31–82			

exposure was lower (OR = 1.26, 95 percent CI 0.66–2.40), and no significant trend was observed for cumulative exposure.

In the subset of workers with known smoking habits (50 cases and 143 controls), the unadjusted exposure odds ratios and trends were similar to the corresponding values in the whole study population. Smoking-adjusted odds ratios for workers simultaneously exposed to cobalt and tungsten carbide (OR = 2.60, 95 percent CI 1.16–5.82) were higher than the crude value (OR = 2.29, 95 percent CI 1.08–4.88), suggesting a slight and negative confounding effect. In this model, the odds ratio for smoking was 3.38 (95 percent CI 1.50–7.62). Inclusion of smoking in the model did not change the trends to any extent. Exploring the interaction between the effect of smoking and exposure to cobalt and tungsten carbide, we found that the odds ratio associated with occupational exposure among ever smokers was higher (OR = 3.62, 95 percent CI 1.35–9.70) than the odds ratio associated with occupational exposure among never smokers (OR = 1.21, 95 percent CI 0.29–4.99). However, inclusion of this interaction in the model did not reach statistical significance ($p = 0.21$). Adjustments for the other potential confounders had little influence on the risk estimates, since adjusted odds ratios for simultaneous exposure to cobalt and tungsten carbide varied between −4 percent and 3 percent from the corresponding crude values, and trends remained unchanged.

DISCUSSION

Exposure assessment

The job-exposure matrix was validated by comparing the semiquantitative exposure estimates from the matrix with available quantitative exposure measurements. Although this comparison was restricted to the years 1971–1994 and to certain workplaces of certain factories, the statistically significant correlation that was observed between the levels assigned by experts and the measured cobalt concentrations validates the job-exposure matrix. This correlation provides a degree of accuracy when extrapolating to earlier years (1942–1971) and to workplaces in the hard-metal production industry for which no measurements were available. We emphasize this correlation considering that the experts had no prior knowledge of the cobalt concentration measurements when assigning the corresponding job-exposure matrix scores (7). In addition, since the introduction of nondifferential misclassifications to a job-exposure matrix is likely to bias odds ratios toward 1.00 (17), the observed dose response with odds ratios far from unity (table 5) could be considered another validation of the scores. However, these measurements were not used to calculate cumulative exposure, because 1) they were taken in certain workplaces of certain factories and only after 1971, and 2) the wide range of cobalt measurements (table 1) clearly signifies that any central statistic is only a crude indication of the cobalt exposure of any given level of the job-exposure matrix.

Subjects and data collection

All French factories producing hard metals were included in the study; therefore, the population that was investigated could be considered an exhaustive sample of those workers exposed. When vital status was assessed, 1,131 subjects were considered lost to follow-up, 875 of whom were born abroad and could not be traced after leaving the factory. This lack of information, which leads to a reduction in statistical power, is unlikely to introduce a bias, as the subjects were censored from the study when lost to follow-up. Furthermore, there is no a priori relation between unknown vital status and cobalt exposure.

Administrative staff and occupational physicians who collected data for the case-control study (job histories and smoking habits) did not know whether they were gathering information on a case or a control. However, they might actually have been aware of the difference, since certain controls were still alive. The sources of information on the job histories of cases and controls were very similar, mainly administrative records. However, because data on smoking were col-

TABLE 5. Lung cancer risk as a function of simultaneous cobalt and tungsten carbide exposure and of other cobalt exposure, in a multiple conditional logistic regression, French cohort of hard-metal workers, 1968–1991

	Simultaneous cobalt and tungsten carbide exposure					Other cobalt exposure*			
	Cases	Controls	OR†	95% CI†	*p* trend	Cases	Controls	OR‡	95% CI
Levels 2–9/levels 0–1	35	81	1.93	1.03–3.62	0.04	15	30	2.21	0.99–4.90
Levels									
0–1	26	99	1.00						
2–3	8	12	3.37	1.19–9.56					
4–5	19	55	1.54	0.76–3.12					
6–9	8	14	2.79	0.96–8.10					
Trend			1.28	0.97–1.68	0.08	15	30	2.05	0.94–4.45
Duration of exposure (levels ≥2)									
Nonexposed	26	99	1.00						
≤10 years	19	52	1.61	0.78–3.34					
10–20 years	12	20	2.77	1.12–6.82					
>20 years	4	9	2.03	0.49–8.51					
Trend			1.47	1.04–2.07	0.03	15	30	2.20	0.99–4.87
Unweighted cumulative doses§									
<32	6	46	1.00						
32–142	16	43	2.64	0.93–7.47					
143–299	16	45	2.59	0.88–7.60					
>299	23	46	4.13	1.49–11.47					
Trend			1.47	1.09–1.97	0.01	15	30	1.83	0.86–3.91
Frequency-weighted cumulative doses§									
<4	8	45	1.00						
4–27	20	45	2.28	0.86–6.06					
27–164	14	45	1.85	0.66–5.20					
>164	19	45	2.73	1.02–7.26					
Trend			1.30	0.97–1.75	0.08	15	30	2.03	0.94–4.39

* Cobalt alone or simultaneously with agents other than tungsten carbide.
† OR, odds ratio; CI, confidence interval.
‡ Odds ratios of workers exposed to other cobalt exposures vs. those nonexposed.
§ Cumulative doses expressed in months × levels.

lected by interview several years after the cases died, the sources of information for cases and controls were different, which might have introduced some differential misclassification.

Nonmalignant respiratory diseases

This study failed to confirm the known pulmonary toxicity of hard metals (18, 19), since the standardized mortality ratios were low for all nonmalignant respiratory diseases except pneumoconiosis (table 3). This lack of effect could be explained by 1) the fact that these diseases are unlikely to cause death, 2) a lack of precise information on death certificates, or 3) simply a lack of statistical power, since expected numbers were low.

Lung cancer

Experiments suggest that the lung toxicity of hard-metal particles containing cobalt and tungsten carbide may result from a specific interaction between cobalt metal and carbide particles that produces activated oxygen species (18–20). These findings may also be relevant to the possible carcinogenicity of hard-metal powders, since an increasing amount of evidence suggests that activated oxygen species can alter the integrity of DNA (21). It has also been demonstrated that cobalt ions can inhibit DNA repair mechanisms (21). Therefore, it is possible that a synergistic mechanism, involving both damage to and inhibited repair of DNA, may be operative as a result of exposure to hard-metal particles. In addition, a report of studies by the US National Toxicology Program (22) provides further evidence of the carcinogenicity of cobalt; in this case, cobalt sulfate heptahydrate was administered to mice and rats for 2 years via inhalation.

Our cohort study showed a 30 percent increase in deaths from lung cancer, which is of borderline statistical significance. This percentage agrees with the results of the few studies published previously. In three Swedish factories, for example, standardized mortality ratios were 1.34 (17 deaths, 95 percent CI 0.77–2.13) in the whole study cohort and 2.78 (7 deaths, 95 percent CI 1.11–5.72) among workers who had more than 10 years of exposure and more than 20 years since first exposure (4). A significant number of deaths from lung cancer was also observed in one French cohort, in which the standardized mortality

ratios were 2.13 (10 deaths, 95 percent CI 1.02–3.93) in the whole cohort and 5.03 (6 deaths, 95 percent CI 1.85–10.95) in the exposed group (5).

The case-control study showed that simultaneous exposure to cobalt and tungsten carbide is associated with a lung cancer risk of about 2.00. This risk increased with increasing exposure estimates. Furthermore, the same level of risk, although of borderline statistical significance, was observed for other heterogeneous cobalt exposures (table 5), ranging from pure cobalt exposure in cobalt powder production workshops to exposure from the other production activities mentioned previously, which were characterized by mixed exposures and the possible presence of potential carcinogens. The only feature common to these different processes was cobalt. Given this heterogeneity, it is difficult to infer a causal relation with the observed lung cancer risk.

The cumulative exposure was computed using 1) an unweighted estimate, which assigned the same value to occasional and full-time exposure, thus favoring peak exposures that occur during activities such as maintenance; and 2) a frequency-weighted exposure, which reduced the effect of occasional exposures. The inclusion of frequency reduced the odds ratios slightly (table 5); this fact suggests that peak exposures, as well as exposures over longer periods, may increase lung cancer risk.

The multiple regression analysis comparing simultaneous exposure to cobalt and tungsten carbide both before sintering and after sintering is of importance, since before-sintering exposure was to powder mixtures, whereas after-sintering exposure was to actual hard metals. However, this analysis was hindered because several workers had been involved in both activities, and the job-exposure matrix assigned both types of exposures to some job titles such as maintenance. The results suggest that the risk due to after-sintering exposure is likely to be lower than that resulting from before-sintering exposure, but the evidence remains weak.

The major possible confounder is smoking. In the cohort study, the observed standardized mortality ratio was in a range (albeit the upper limit) that could be explained by the confounding effects of tobacco smoking (23). However, the mortality from other tobacco-related diseases (24) was below the rate expected, which excludes an overall increase in the incidence of smoking as compared with the reference population (table 3) (25). In the case-control study, the risk associated with smoking (OR = 3.38) seemed lower than that expected. We acknowledge the possibility of misclassification, particularly among the nearly 20 percent of nonsmoking cases. Yet, subjects who were classified as nonsmokers by former colleagues were unlikely to have been heavy or longtime smokers. Moreover, the ever-smoker category also included former and light smokers. Adjusting for smoking did not change the exposure odds ratios, which suggests that ever smoking is not related to exposure and is not a confounder. After adjustment for ever smoking, residual confounding by smoking would occur if, among smokers, exposure were related to quantitative smoking.

The only sketchy data we have on this association are the number of former smokers, although we do not know when each individual was coded as such. A slight evidence of association exists, as the number of former smokers among ever smokers was marginally higher among the nonexposed than among the exposed, but this finding cannot explain the observed risks. On the other hand, the number of former smokers among cases (but not among controls) was the lowest in the highest cumulative exposure category. This result points to a possible interaction between smoking and occupational exposure. This hypothesis is confirmed in the results showing that an occupational risk is observed mainly among smokers. However, this interaction is not statistically significant and relies on the absence of misclassification. It should therefore be interpreted with caution.

In conclusion, this study showed a statistically significant increased mortality from lung cancer among workers exposed simultaneously to cobalt and tungsten carbide when manufacturing hard metals. This excess is unlikely to be due to confounding by smoking.

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