

Cancer Incidence Among Hardmetal Production Workers

The Swedish Cohort

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The cancer incidence was determined for 3713 workers from three plants from 1958 to 2011. The exposure measures were ever/never exposed, duration, cumulative, and mean cobalt concentrations. The incidence of all malignant neoplasms was increased at one plant, but standardized incidence ratio (SIR) was 0.96 for all workers. Lung cancer incidence was increased for all workers, SIR 1.38 (1.01 to 1.85). The lung cancer incidence was associated with shorter employment time and showed no exposure–response. There was decreased incidence for skin cancer. Increased lip cancer incidence found at one of the production plants might be related to diagnostic intensity. Lung cancer incidence showed no correlation to cobalt exposure based on internal comparison. The increased SIR for all workers might be associated with other factors.

Occupational exposure to cobalt is well established in the hardmetal industry, which produces cutting tools that are mainly used for manufacturing of industrial products and parts. Hardmetal is a group of composite materials that consists predominantly of the hard tungsten carbide (WC) particulate phase tied together with cobalt as a binder.¹ Nickel in the metallic state could also be added.

Exposure to cobalt during the production of hardmetal has been associated with several adverse health effects, such as rhinitis, sinusitis, bronchitis,² asthma,^{3,4} and other respiratory effects,⁵ that is, dose-related decreased lung function over time,⁶ and hardmetal lung disease (HMLD).⁷ Allergic dermatitis has also been reported,^{4,7} as well as cases of cardiomyopathy,^{8,9} and an increased incidence of ischemic heart disease were determined in a cohort study of hardmetal workers.¹⁰

Mortality with special reference to lung cancer has been investigated in a number of epidemiological studies. A French cohort of hardmetal workers based on 709 male workers and mortality followed from 1956 to 1989 showed no overall increased

mortality; however, for lung cancer, a Standard Mortality Ratio (SMR) of 2.1 was determined.¹¹ Another French cohort study that investigated the relationship between hardmetal work and lung cancer based on data from one site with 3398 male and female workers between 1968 and 1998 showed a small rise in total mortality, and an elevated risk for male lung cancer associated with exposure (SMR 1.7).¹² Furthermore, a nested case–control study that included data from 10 French hardmetal sites between 1968 and 1991 showed increased total mortality, and determined an odds ratio (OR) of 1.9 from the 68 cases of lung cancer.¹³ A Swedish cohort study based on 3163 males from three hardmetal plants followed up regarding mortality from 1951 to 1982 showed no increased overall mortality (SMR 0.96), but identified a significant excess lung cancer risk (SMR 2.8) for the overall exposed group (including both high and low exposed workers), workers with duration of exposure more than 10 years, and with latency of more than 20 years, based on seven cases (10).

The International Agency for Research on Cancer (IARC) has classified cobalt metal with tungsten as probably carcinogenic to humans (group 2A).¹⁴ The harmonized classification for cobalt within EU legislation¹⁵ does not address the carcinogenicity; however, on the basis of animal testing of cobalt, the industry self-classification states that cobalt may cause cancer *by inhalation*.¹⁶ Regarding metallic nickel, IARC classifies metallic nickel as possibly carcinogenic to humans (group 2B).¹⁷ Results of other country-specific cohort analysis and exposure assessment are presented in the same volume of this journal as a series of companion papers (Kennedy et al, submitted; McElvenny et al, submitted; Morfeldt et al, submitted; Mosshammer et al, submitted; Marsh et al, accepted for publication JOEM 2017).

The present study investigates how exposure to cobalt, nickel, and tungsten for three Swedish hardmetal plants operating from the 1930s and onwards affects morbidity, with a special reference to lung cancer.

METHODS

Study Objects and Processes

Three major Swedish hardmetal production sites were included; companies A and B were rurally located and company C located in an urban area. These companies are currently employing approximately 1340, 1440, and 350 white and blue-collar workers, respectively. They began operating in 1931, 1951, and 1942, respectively, and mainly produce inserts used as cutting tools or drills, and one of the units also produces big parts, such as rolls for hot rolling.

The production of hardmetal tools consists of several steps, the first being formation of tungsten carbide (WC) from tungsten oxide and elementary carbon through carburization to form WC powder. Next, the tungsten carbide is mixed with cobalt powders, followed by granulation. After granulation, the material is pressed, pre-sintered (heated), and then accurately machined into the desired shapes. Pre-sintering was abandoned in the mid-70s. The pieces are finally sintered at 1400°C to 1500°C to reach the hardness that is close to that of diamond. The products are then ground and often coated, and as a last step, the finished products are inspected for quality, stored, and shipped out of the plant.

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The hardness and abrasive wear increases when either cobalt content or grain size decreases; a grain particle diameter between 0.1 and 5 μm and a cobalt content of 2% to 14% are common today (1). Nickel may be used as binder metal for some applications and in cermets, often together with cobalt. The nickel concentration levels generally vary between 6% and 14%. Chromium carbide is also used in the production of some hardmetal products.

The Cohort (Study Population) and Cohort Follow-up

All three Swedish hardmetal sites were included and data were extracted from the personnel files. Data included site, name, complete personal identification numbers, that is, year of birth, and duration of employment, with the year of start and end at defined departments and/or jobs.

We started from an initial cohort in total, 16,999 blue and white-collar workers who were matched to the Swedish Population Register. However, 1366 workers were excluded due to unclear or missing personal ID or duration of employment, leaving 15,633 workers for matching and analysis. For cancer incidence, we selected blue-collar workers with at least 1 year employment time, in total 3728 individuals. Cancer incidence data in Sweden exist from 1958, hosted by the National Board of Social Health and Welfare. Matching to the cancer registry was done for 1958 to 2011. Fifteen workers were excluded because they were dead before 1958 or started at the plants after 2011.

The 2545 male and 1168 female workers were distributed between companies A (1193), B (1790), and C (730) (Table 1). The cohort included old members, the earliest year of birth ranging from 1896 to 1906, and the corresponding median ranging from 1939 to 1963. The average duration of employment was 12, 15, and 9 years at companies A, B, C, respectively. The total number of person years was 108,152, unevenly distributed between the different sites.

The cancer incidences were compared with national Swedish rates covered the period 1958 to 2011. The cancer data were coded according to the International Classification of Disease (ICD 7).

Exposure Assessment and Measurement Database

The job or departmental class for each worker and time period were extracted from the personnel files and compared with company classification, which varied between different time periods in resolution. In the international study, some 65 job or departmental classes were identified. All workers were assigned a job class according to classifications from the international study. For the Swedish cohort, aggregated job classes were defined on the basis of similar exposure group (SEG) considerations and measurement data, leaving the following aggregated job classes A-I for exposure-response analysis.¹⁸ Job class A was defined as background (unexposed, ie, office workers), B as intermittent low (foremen, engineers, material handler, assembly, mark, pack, inspection, and packing), C as intermittent high (lab R&D, maintenance), D as

powder production (weighing, mixing, spray dry, packaging), E as pressing, (pressing, forming, shaping), F as slow moving operations, G as coating, H as rolls (big pieces), and I as grinding.

Personal and area air measurement data were extracted from company records, covering a time period from the early 1970 to 2012.

The sampling of the total dust was carried out according to a modified version of National Institute of Occupational Safety and Health Manual of Analytical Methods 0500¹⁹ using an open-faced cassette (OFC) with a 25 mm cellulose acetate filter (Millipore 3 μm pore size) and an airflow of 2.0 L/min. Inhalable dust was collected using a GSP filter head (GSA Messgeräteebau GmbH, Gut Vellbrüggen, Germany) with a 37 mm cellulose acetate filter (Sartorius Stedim 8 μm pore size) connected to a pump (GSA SG4000; Messgeräteebau GmbH, Gut Vellbrüggen, Germany), operated at an air flow of 3.5 L/min.²⁰ Determination of the mass of dust on the filters was made gravimetrically.

The vast majority of the samples in the measurement database were collected as total dust levels, with the metals subsequently determined in that particle fraction. The database constituted included a total of 2693 personal measurements. The majority of the personal samples represented cobalt, tungsten, and nickel, that is, 1230 cobalt, 313 nickel, and 342 tungsten measurements.

The analysis of metals was carried out using different techniques. From the 1970s up to 1992, atomic absorption spectroscopy (AAS), predominantly with an LOQ of 1 μg /sample,²¹ was used. From 1992 to 2006, X-ray fluorescence (XRF), with much the same LOQ level, was used.²² Such analysis did not require any dissolving of the sample, thus allowing for multiple analyses including wet chemistry. From 2006 and up to 2011, inductive coupled plasma spectroscopy (ICP) was used, and from 2011 onward, low-resolution ICP using mass spectroscopy for identification and quantification with an LOQ 0.05 μg /sample²³ was primarily used.

Exposure Measures and Modeling

The standard exposure measures used were ever/never exposed, duration of employment, cumulative, and mean exposure. Latency time was defined as the period between first exposure and the observation. In addition, we used data from a log-linear model analysis of air concentrations to calculate cumulative and mean cobalt exposure measures, expressed as mg/m^3 years and mg/m^3 , respectively. In our model analysis, we used data from our measurement database to determine the exposure concentrations for different time periods, sites, and aggregated job titles. Our model initially included five different time periods (1970 to 1979, 1980 to 1989, 1990 to 1999, 2000 to 2009, 2010+), three different sites, and nine categories of aggregated job titles as independent variables. No data were available for the time period 1958 to 1969, during which a large number of the studied workers were exposed. We used a standard exposure assessment procedure; the time period before 1970 would have the same modeled exposure as the period 1970 to 1979.

Exposure to cobalt was defined as cumulative exposure mg/m^3 year (ie, exposure level times exposure time) and mean (cumulative exposure divided by duration of exposure) and categorized in two different ways. The determined cumulative and mean exposures were categorized as quartiles, for both the total cohort and for blue-collar workers. Exposure was also categorized into three groups that reflected exposures relevant to a 40-year of working at the present Swedish Occupational Exposure Limits (SOEL), that is, 0.02 mg/m^3 , defined as the 8-hour time-weighted average air concentration (8-hour TWA). The cumulative dose values for the three categories were 0.20 or less (low), 0.21 to 0.40 (medium), and at least 0.41 (high) mg/m^3 year. The high exposure group reflects half of the maximum allowed life-time exposure to cobalt, 0.8 mg/m^3 year, which corresponds to 40 years of exposure at the present Swedish

TABLE 1. Study Population, Blue-Collar Workers Total and by Plant

Study Population	A	B	C	Total	Person-years
Personnel files					
Men	689	1,278	578	2,545	72,378
Women	504	512	152	1,168	35,774
Total	1,193	1,790	730	3,713	108,152
Register matching					
Emigrated	10	44	35	89	
Alive	1,077	1,382	360	2,819	
Dead	106	364	335	805	

OEL for cobalt, 0.02 mg/m^3 .²⁴ The corresponding classes based on means would be 0.005 or less, 0.0051 to 0.010, and more than 0.010 mg/m^3 .

We present exposure–response morbidity in particular that of lung cancer, based on the following exposure measures: ever/never exposed; duration of exposure including latency; cumulative cobalt exposures ($\text{mg/m}^3 \cdot \text{year}$), and mean cobalt exposure (mg/m^3). For nickel and tungsten, a dichotomized exposure classification will be presented and exposure–response analyzed based on cumulative exposure.

Smoking Data

A questionnaire regarding smoking habits was distributed to cohort workers who were alive and to the next of kin to cohort members who had died. The questionnaire had questions whether the worker was a smoker, nonsmoker, or ex-smoker, as well as the duration and time period of their smoking. In addition, questions regarding jobs other than those in the hardmetal industry, but which were associated with exposures and jobs associated with lung cancer, such as quarrying, stainless steel welding, chimney sweepers, coke oven plant workers, iron and steel foundry workers, ship yard workers, insulators, and asbestos cement workers, were included. The postal questionnaire was distributed to 8992 living cohort members and also to the next of kin for 1473 cohort members who had died after 1991. The possibility to trace next of kin was limited to those workers who had died after 1991, because as of 1991, the Swedish Tax Agency implemented a data system for the Swedish Population Register based on complete personal identification information available to us. Smoking data were obtained for 31% of the living workers and 17% for the deceased through next of kin.

Initially, after adding smoking data to our cohort, another matching would be performed, and if possible, a nested case–control study including smoking habits was then performed. However, the response rates and representativeness, in particular for the deceased, were too poor both in number and representativeness to enable a proper nested case–control study. Smoking data were therefore used to discuss smoking habits in the different exposure estimates derived from our Cox proportional hazard regression analysis.

Statistical Methods

Cause-specific morbidity data coded in ICD7 were used to calculate national-based standardized incidence ratios (SIRs), which were obtained by comparing the cohort morbidity with that of the general population of Sweden between 1958 and 2011 and expressed as ratios of observed and expected incidence. The expected numbers of deaths were calculated by multiplying person-years by gender, 5-year age group, calendar year, and cause-specific morbidity rates of the general Swedish population. These calculations were carried out using Stata Statistical Software (version 12.0; Stat Corp College Station, TX). The 95% confidence intervals (95% CI) for the SIRs were computed assuming a Poisson distribution of the observed numbers of cases. We have analyzed cancer incidence using selected ICD codes, and paid particular attention for lung cancer. The exposure measures were ever/never exposed, duration of exposure including latency, and cumulative and mean exposure for the total workforce, in particular blue-collar workers. The exposures were stratified on three exposure groups and exposure quartiles.

A Cox proportional hazard regression analysis (Stata Statistical Software, version 12) was performed on the basis of cumulative and mean exposure, adjusted for year of birth (categorized in 10-year age bands), duration of employment, and gender to analyze the exposure–response relation between lung cancer and cumulative and mean cobalt.

RESULTS

Exposure Assessment

Measurement Data

The personal and area air measurement data were extracted from company records, covering a time period from early 1970 to 2012. The majority of the samples represented cobalt, tungsten, and nickel, with 1230, 313, and 342 exposure measurements for cobalt, nickel, and tungsten, respectively. The cobalt concentration levels varied between 0.0001 and 2.8 mg/m^3 , with median and arithmetic mean values of 0.01 and 0.04 mg/m^3 , respectively. Nickel exposure levels ranged from 0.0001 to 2.8 mg/m^3 . Of the cobalt concentrations, 37% exceeded 0.02 mg/m^3 , and 21% exceeded 0.04 mg/m^3 . On the contrary, only 6% of nickel measurements exceeded 0.1 mg/m^3 and only 1% exceeded 0.5 mg/m^3 . The personal cobalt exposure levels, organized by time period and aggregated job titles, are summarized in Table 2. The Swedish OELs for cobalt and nickel in the metal state are currently 0.02 and 0.5 mg/m^3 , respectively. Cobalt is considered a carcinogen in Sweden.¹⁹

Exposure Modeling and Exposure Measures

Log-linear modeling was performed for all aggregated jobs and the time period 1950 to 2012. Estimates for time periods when measurement data were sparse were based on two different assumptions: (1) data from 1970 to 1979 were used to assess exposure for earlier time periods (1950 to 1969); and (2) exposures for the two time periods 1950 to 1959 and 1960 to 1969 were estimated by linear extrapolating for each job class. Detailed data regarding modeling and exposure measures will be presented later. Data from modeling based on measurements 1970 and onwards are presented (Table 3). The modeling, with 1970 as the reference, mainly reflects declining exposures with time, as well as exposure relations between different job classes related to grinding.

The regression coefficients (ln B-values) calculated for the job codes between 1950 and 1959 and 1960 and 1969 based on our regression model and linear extrapolation were 0.45 and 0.25, respectively, and used in our analysis.

The determined cobalt air concentrations were then used to calculate cumulative and mean cobalt exposures in $\text{mg/m}^3 \cdot \text{years}$ and mg/m^3 , for 3728 blue-collar workers with more than 1 year of exposure presented by job class (Table 4). The average cumulative exposure was $0.084 \text{ mg/m}^3 \cdot \text{years}$, corresponding to a daily exposure of 0.004 mg/m^3 for 20 years of exposure. The jobs showing high cumulative doses were determined at powder, pressing, and rolls production. The same pattern was evident in the mean exposure measure.

CANCER INCIDENCE

All Malignant Neoplasms

Table 5 presents the overall cancer incidence for the whole cohort using ICD 7 diagnosis coding, which were then compared with national rates. A total of 437 cases were observed. The SIR of all malignant neoplasms was calculated to 0.96 (95% CI 0.88 to 1.06). However, the overall incidence varied between companies, and company C was the only company to show a significantly increased SIR 1.23 (95% CI 1.05 to 1.45), as the SIRs for companies A and B the SIRs were 0.79 and 0.87, respectively. The incidence ratio for primary bronchus and lung cancer (162.1) was increased SIR 1.38 (95% CI 1.01 to 1.85). A negative exposure–response pattern was identified when lung cancer mortality was stratified based on duration of exposure (Table 6). We found significant under risks for malignant melanoma (ICD 190) and skin cancer excluding melanoma (ICD 191). There was an increased incidence of lip

TABLE 2. Cobalt Exposure (mg/m³) by Time Period and Aggregated Job Classes (Blue Collar)

Job Class	1980–1989						Total
	1969	1970–1979	n AM Range	1990–1999	2000–2009	2010+	
Powder		68	79	128	170	46	491
		0.081	0.15	0.074	0.017	0.014	0.062
Pressing		0.0070–0.54	0.0071–2.8	<0.001–0.6	<0.001–0.24	<0.001–0.05	<0.001–2.78
		47	54	98	170	53	422
Slow moving op		0.066	0.048	0.052	0.0070	0.0069	0.029
		<0.001–0.69	0.002–0.65	<0.001–1.6	<0.001–0.096	<0.001–0.038	<0.001–1.6
Coating			6	9	3	8	26
			0.0045	0.081	0.0099	0.001	0.030
Rolls			0.001–0.01	0.001–0.68	<0.001–0.025	<0.001–0.002	0.001–0.68
		1	2	2	13	3	19
Grinding		0.002	0.001	0.001	0.001	<0.001	0.001
			0.001–0.001	<0.001–0.005	<0.001–0.001	<0.001–0.001	<0.001–0.001
Total*		4	2	1	24	3	34
		0.02	0.23	0.032	0.023	0.010	0.033
Grinding		0.01–0.03	0.03		0.001–0.11	0.003–0.023	0.001–0.42
	3	33	58	15	20	10	139
Total*	0.006	0.012	0.040	0.027	0.0037	0.0051	0.025
	0.002–0.01	<0.001–0.08	<0.001–0.67	0.002–0.16	<0.001–0.037	<0.001–0.025	<0.001–0.67
Total*	3	168	212	265	424	138	1,210
	0.0057	0.056	0.083	0.060	0.011	0.0091	0.041
	0.002–0.01	<0.001–0.69	<0.001–2.78	<0.001–1.6	<0.001–0.24	<0.001–0.13	<0.001–2.78

*All job titles.

cancer for blue-collar workers at one of the plants SIR 4.50 (95% CI 1.23 to 11.53; Table 5).

Cumulative and Mean Exposure

There is a significant increased risk for lung cancer for all workers, SIR 1.38 (95% CI 1.01 to 1.85) (Table 5). When the cumulative exposure was analyzed by quartiles, SIRs were 1.80, 1.34, 0.79, and 1.68*. When the exposure was stratified based on exposure classes, that is, cumulative doses reflecting a 40-year working life at 0.01 mg/m³, the SIRs were 1.40, 0.75, 2.06, and nonsignificant (Table 7). Similar patterns were identified when lung cancer incidence was analyzed by mean exposures; however, a statistically significant increased SIR was determined for the highest exposure class.

Cox Regression

Cox proportional hazard regression was performed for internal comparison. The data are presented as hazard ratios for different cumulative and mean exposure groups, adjusted for year of birth and duration of exposure. The hazard ratios ranged from 0.33 to 1.9 for all aggregated jobs more than 1 year of exposure; however, none of the hazard ratios were statistically significant (Table 8). Our high exposure estimates as analyzed by quartiles for cumulative exposures and means were rather low, for the cumulative exposure 0.088+ mg/m³years and 0.0089+ mg/m³.

Smoking Data

A response rate of 31% (total number of answered questionnaires, 2746; distributed 8992) was achieved from the questionnaires distributed to the living persons in the cohort, and the average percentage of smokers in this group was 45% (data not in table). The corresponding figures for the deceased members were 17% (245; distributed 1473) and 59% smokers. When smoking habits were analyzed by duration of exposure in five groups, from less than 1 year to more than 20 years, the percentage of smokers in the groups ranged from 41% to 48%, with an average of 46%. Among the short-term workers, less than 1 year of exposure 48%

were smokers, that is, this group did not differ much from worker with more than 1 year of exposure.

When the analysis was restricted to blue-collar workers with more than 1 year of exposure, and evaluated year of birth by decades from the 1930s to 1990, the overall percentage of smokers ranged from 65% to 27%. When job class was included, results range were powder from 25% to 63%, pressing 11% to 72%, slow moving operations 23% to 70%, coating 22% to 75%, and grinding 20% and 59%.

TABLE 3. Exposure Modeling Based on Log Linear Multiple Regression and Measurement Database 1970 and Onwards for Blue-Collar Workers

	B	P	95% CI	
(Constant)	0.004	<0.001	0.003	0.006
Company				
A ref*	1			
B	1.896	<0.001	1.474	2.438
C	2.440	<0.001	1.872	3.177
Year				
1970–1979 ref*	1			
1980–1989	1.089	0.568	0.813	1.458
1990–1999	0.843	0.237	0.635	1.120
2000–2009	0.229	<0.001	0.172	0.304
2010+	0.194	<0.001	0.137	0.274
Job class				
Grinding ref*	1			
Powder	5.468	<0.001	4.158	7.192
Pressing	2.079	<0.001	1.578	2.740
Slow moving	0.620	0.111	0.344	1.116
Coating	0.224	<0.001	0.114	0.441
Rolls production	4.759	<0.001	2.724	8.306

95% CI, 95% confidence interval; B, regression coefficient; P, P < 0.05.

*Reference category.

TABLE 4. Cumulative and Mean Exposure, Blue-Collar Workers, > 1 Year for All Jobs, Model Data for 1970–2012, Extrapolated Data for 1950–1970

Job Class	N	Cumulative Exposure, mg/m ³ year				Mean, mg/m ³			
		Mean	Median	Min	Max	Mean	Median	Min	Max
Several jobs	533	0.085	0.052	0.0011	0.91	0.0055	0.0028	0.000047	0.052
Powder	257	0.30	0.16	0.00028	3.13	0.036	0.044	0.00012	0.081
Pressing	726	0.11	0.049	0.000084	1.05	0.012	0.010	0.000013	0.031
Slow moving operations	224	0.035	0.018	0.00056	0.25	0.005	0.0053	0.000059	0.0092
Coating	243	0.0083	0.0042	0.000006	0.05	0.0007	0.0004	0.0000015	0.0021
Rolls production	57	0.33	0.18	0.011	1.72	0.025	0.021	0.00027	0.049
Grinding	1,673	0.049	0.024	0.000087	0.44	0.0045	0.0035	0.0000070	0.017
Total	3,713	0.085	0.033	0.000006	3.13	0.0084	0.0038	0.0000015	0.081

DISCUSSION

Our cohort of Swedish hardmetal showed a significant excess cancer incidence for all malignant neoplasms and lung cancer. The increased incidence was associated with the short-term workers and one of the plants. For lung cancer, we found no exposure–response through an internal comparison analysis using Cox proportional hazard regression.

Personal Data and Register Qualities

Our cohort encompasses a fair number of exposed workers and person years, and thus provides a sufficient number for exposure–response analysis.

The Swedish Population and National Cancer registers are well known for their quality, and they use personal identification numbers to enable national and regional tracking.²⁵ We have evaluated mortality patterns in the cohort by time period to ensure the completeness of the company personnel registers. Lost to follow-up due to missing personal identification number or incomplete date of employment was only about 10%; all of the cohort members for mortality analysis were identified in the mortality registers.

Exposure Assessment and Exposure Measures

We have used standard exposure measures to evaluate our cohort (ever/never exposed, duration of exposure including latency, and cumulative and mean cobalt exposure) for exposure–response analysis.^{26,27} It is important to note that, when cumulative dose is strongly related to the duration of exposure or other mechanisms related to high exposure at shorter time periods, it is also useful to include mean as an exposure measure.²⁸ Our aggregated job classes reflect the job titles occurring in the company data files and registers accurately, as do data in our historical measurement database. Our quantitative cobalt exposure measures are based on log linear modeling, including company, job class, and time period by decade, from 1970.²⁹ A significant group of our cohort was included in the cancer registers starting 1958; we have used our modeling of cobalt exposure to estimate the periods 1958 to 1959 and 1960 to 1969 rather than applying data from 1970 to 1979 for these earlier years. Our model shows decreasing exposure concentration levels at a rate of 2% to 3% per year, in line with trends reported in several other industrial cohorts.^{30,31}

Lung Cancer and Exposure to Cobalt

We have presented incidence data using national rates for morbidity even though two of the plants are rurally located, and one urban. In our mortality study, we made another comparison using regional rates, defined as either local county or city based on where

plants were located. The expected numbers were calculated by multiplying person-years by gender, 5-year age group, calendar year, and cause-specific incidence rates of the general Swedish population. We found limited effects only using regional rates for mortality in all cancer as well as for lung cancer. We therefore abstain from using regional rates in the present study focusing on morbidity, as any differences between incidence for national and regional rates are likely modest and insignificant.

Our initial analysis of lung cancer risk based on duration of exposure and latency showed an almost negative exposure–response, even though all but one of the SIRs exceeded 1 (and were nonsignificant). Given the age of the cohort, we still have a large number of lung cancer cases, $n=45$. This supports the robustness of our lung cancer data.

We have analyzed dose–response by SIR using two different dose groups for the cumulative and mean exposures measures, one based on quartiles and the other based on exposure grouping (low, medium, and high) related to 40 years exposure at 50% of the current Swedish OEL, 0.02 mg/m³. The latter grouping was performed for reasons of comparison with the earlier studies and OELs, in particular the Swedish study (10).

The analysis for all workers gives us a significant risk for lung cancer (SIR 1.38), and an exposure–response pattern including a significant SIR for the fourth quartile, of cumulative dose corresponding to average exposure more than 0.0022 mg/m³ for 40 years. We consider cumulative dose measures the most relevant for lung cancer.

Our data were not adjusted for smoking, nor have we adjusted for differences in socioeconomic or lifestyle factors, that is, we are still comparing our data with the national population. These issues, as well as the data from our questionnaires, are discussed in separate paragraphs. However, the lack of individual smoking data and other potential differences between our hardmetal workers and the general population necessitates an internal comparison, and is why we performed a Cox proportional hazard regression analysis (Table 8). No statistically significant increased hazard ratios (hazard ratios > 1) were determined for cumulative or mean exposures, when the analysis included all jobs. Our exposure grouping initially used quartiles, the highest cumulative exposure group representing 0.002 mg/m³ for 44 years. The hazard ratio exceeded 1 for the highest quartiles for cumulative but not mean exposure measures. The evaluation of exposure–response analyses for the exposure measures ever/never employed, duration of exposure, cumulative and mean exposure to cobalt, and comparing our lung cancer incidence with the general population, and an internal comparison fail to provide a consistent exposure–response relationship.

TABLE 5. Cancer Incidence 1958–2011, ICD Code, 7th Revision, Blue-Collar Workers

ICD7	Cause of Cancer Diagnosis		Obs	Exp	SIR	95% Low	95% Upper
	All malignant neoplasms	Total	437	453	0.96	0.88	1.06
		A	63	80	0.79	0.61	1.01
		B	205	236	0.87	0.75	1.00
		C	169	138	1.23*	1.05	1.43
140	Lip	Total	5	1.8	2.76	0.90	6.44
		A	0	0.2			
		B	4	0.9	4.50*	1.23	11.53
		C	1	0.7	1.45	0.04	8.09
153	Colon	Total	35	30.0	1.17	0.81	1.62
		A	6	4.8	1.26	0.46	2.75
		B	16	15.4	1.04	0.59	1.68
		C	13	9.8	1.33	0.71	2.27
154	Rectum anus	Total	15	18.5	0.81	0.45	1.34
		A	2	2.9	0.70	0.08	2.52
		B	9	9.6	0.94	0.43	1.78
		C	4	6.1	0.66	0.18	1.69
157	Pancreas	Total	11	9.7	1.13	0.57	2.03
		A	2	1.5	1.37	0.17	4.96
		B	5	4.9	1.02	0.33	2.38
		C	4	3.3	1.20	0.33	3.06
161	Larynx	Total	5	2.6	1.9	0.62	4.44
					0		
		A	1	0.3	3.09	0.08	17.22
		B	1	1.4	0.74	0.02	4.09
		C	3	0.9	3.19	0.66	9.32
162.1	Bronchus and lung, primary	Total	45	32.6	1.38*	1.01	1.85
		A	4	4.8	0.84	0.23	2.15
		B	24	17.1	1.40	0.90	2.09
		C	17	10.7	1.59	0.92	2.54
162	Trachea, bronchus, lung and pleura, primary	Total	45	34.0	1.33	0.97	1.77
		A	4	5.0	0.81	0.22	2.08
		B	24	18.0	1.34	0.86	2.00
		C	17	11.2	1.52	0.89	2.43
162.2	Pleura	Total	0	1.28			
		A	0	0.15			
		B	0	0.70			
		C	0	0.44			
177	Prostate	Total	74	80.3	0.92	0.72	1.16
		A	6	9.0	0.67	0.25	1.47
		B	40	43.8	0.91	0.65	1.24
		C	28	27.6	1.02	0.67	1.47
1810	Urinary bladder	Total	22	21.5	1.02	0.64	1.55
		A	2	2.7	0.73	0.09	2.63
		B	8	11.3	0.71	0.31	1.39
		C	12	7.5	T	0.83	2.80
190	Malignant melanoma of skin	Total	10	21.0	0.48*	0.23	0.87
		A	2	4.7	0.43	0.05	1.54
		B	6	11.1	0.54	0.20	1.18
		C	2	5.2	0.38	0.05	1.38
191	Skin (melanoma excluded)	Total	8	22.5	0.36*	0.15	0.70
		A	0	3.3			
		B	2	11.8	0.17	0.02	0.61
		C	6	7.4	0.81	0.30	1.76
200	Lymphosarcoma and reticulosarcoma	Total	14	13.7	1.02	0.56	1.71
		A	0	2.3			
		B	9	7.2			
		C	5	4.2	1.20	0.39	2.80
203	Multiple myeloma plasmocytoma	Total	7	5.5	1.26	0.51	2.60
		A	0	0.8			
		B	3	2.9	1.05	0.22	3.06
		C	4	1.84	2.18	0.59	5.58

95% CI, 95% confidence interval; Exp, expected cases; Obs, observed cases; SIR, standardized incidence rate.

* $P < 0.05$.

TABLE 6. Lung Cancer Incidence, ICD Code 162.1, 7th revision, SIR and 95% Confidence Intervals, Total and by Plant, Duration of Exposure, and Latency

	Latency Years	Duration of Exposure, Years	Obs	Exp	SIR	95% CI
Total	<20	≤20	11	6.57	1.67	0.83–2.99
		20+	1	1.22	0.82	0.02–4.55
	20+	≤20	22	15.44	1.43	0.89–2.16
		20+	11	9.36	1.17	0.59–2.10
A	<20	≤20	0	0.97		
		20+	0	0.29		
	20+	≤20	3	1.5	2.01	0.42–5.88
		20+	1	2.0	0.50	0.01–2.76
B	<20	≤20	5	3.54	1.41	0.46–3.29
		20+	0	0.69		
	20+	≤20	10	7.49	1.34	0.64–2.46
		20+	9	5.41	1.66	0.76–3.16
C	<20	≤20	6	2.07	2.90*	1.06–6.32
		20+	1	0.25	3.98	0.10–22.2
	20+	≤20	9	6.46	1.39	0.64–2.64
		20+	1	1.94	0.52	0.01–2.87

95% CI, 95% confidence interval; Exp, expected cases; Obs, observed cases; SIR, standardized incidence rate.
*P < 0.05.

Other Cancer

The incidence of all malignant neoplasms was significantly increased, at one of the plants but SIR was 0.96 (0.88 to 1.06) for all blue-collar workers. This indicates that it is probably related to factors other than cobalt. This factor can be specific for the exposure or population at the plant located in the urban area. We found no increased incidence for melanoma, ICD 190, nor for skin cancer without melanoma ICD 191. There was also an increased incidence of lip cancer at one of the rural plants but not for all blue-collar workers. Increased lip cancer has to our knowledge not been reported before. It is not much related to increased mortality, which means that it will probably not be detected using mortality studies. Health outcomes that are not related to severe effects might, on the contrary, be sensitive to diagnostic bias. The workers at the plant with increased incidence have had problems with effects on skin such as eczema. Our results might be caused by such diagnostic bias or it might be a true effect from hardmetal exposure.

Smoking

Tobacco smoke, tobacco smoking, and involuntary smoking are all considered to be carcinogenic (group 1) to humans.³²

To obtain more information regarding smoking habits, we used questionnaires, distributed to living cohort members with a response rate of 31%, and an average percentage of smokers of 45%. The corresponding figures for the deceased cohort members were 17% and 59%, respectively. Among the short-term workers with less than 1 year of exposure, 48% were smokers; this group did not differ much from workers with more than 1 year of exposure. We consider the response rates poor, and our intentions to use questionnaire data for individual smoking data in a case-control study or other adjustments were not possible.

However, we used our data on smoking habits to compare the reference and the exposure groups regarding smoking habits, in particular, if excess hazard ratios were determined through the Cox regression analysis.

TABLE 7. Lung Cancer Incidence Code 162.1 All Jobs Exposed, Total, >1 Year of Exposure, Exposure Modeling With Cumulative Exposures, and Means for Job Codes 1959 = (LN) 0.45 och 1960–1969 0.25, Total and By Different Coexposure Including Quartiles

	Cumulative Exposure, mg/m ³ * years				Mean Exposure, mg/m ³					
	Obs	Exp	SIR	95% CI	Obs	Exp	SIR	95% CI		
Total	45	32.6	1.38*	(1.01–1.85)	45	32.6	1.38*	(1.01–1.85)		
Co exp class	Exposure mg/m ³ * years				Exposure mg/m ³					
	≤0.20	36	25.70	1.40	(0.98–1.94)	≤0.0050	10	10.63	0.94	(0.45–1.73)
	0.21–0.40	3	3.99	0.75	(0.15–2.19)	0.0051–0.010	13	9.81	1.33	(0.71–2.27)
Co exp quartiles	0.41+	6	2.91	2.06	(0.76–4.49)	0.011+	22	12.17	1.81*	(1.13–2.74)
	≤0.010	6	3.33	1.80	(0.66–3.92)	≤0.001	3	3.79	0.79	(0.16–2.31)
	0.011–0.033	9	6.72	1.34	(0.61–2.54)	0.002–0.0038	5	4.69	1.07	(0.35–2.49)
	0.034–0.087	7	8.86	0.79	(0.32–1.63)	0.0039–0.0088	10	8.76	1.14	(0.55–2.10)
	0.088+	23	13.70	1.68*	(1.06–2.52)	0.0089+	27	15.4	1.76*	(1.16–2.56)

95% CI, 95% confidence interval; Exp, expected cases; Obs, observed cases; SIR, standardized mortality rate.
*P < 0.05.

TABLE 8. Lung Cancer Incidence, Cox Proportional Hazard Regression All Jobs >1 Year of Exposure, Cumulative and Mean Exposures by Quartiles

	Cumulative Exposure, mg/m ³ .years			Mean Exposure, mg/m ³		
	HR	95% CI	P	HR	95% CI	P
Exposure mg/m ³ years				Exposure mg/m ³		
< 0.01	1			<0.001	1	
0.011–0.033	1.9	(0.20–18.5)	0.58	0.002–0.0038	0.33	(0.05–2.34)
0.034–0.087	1.0	(0.13–8.0)	0.99	0.0039–0.0088	0.77	(0.15–3.9)
0.088+	1.6	(0.22–12)	0.64	0.0089+	0.96	(0.22–4.3)

Adjusted for year of birth and duration of exposure.
95% CI, 95% confidence interval; HR, hazard ratio.

Other Studies

Our findings show a similar mortality pattern to the earlier published data from an original cohort of Swedish hardmetal workers (3163 male workers), evaluated for the period 1940 to 1982.¹⁰ They used four exposure categories, with the high exposure group for cobalt (powder production) included TWAs ranging from 60 to 11,000 $\mu\text{g}/\text{m}^3$ during the study period, and the low exposure group ranging from 1 to 2 $\mu\text{g}/\text{m}^3$; however, these were not used quantitatively. The overall mortality was found to be less than 1. However, when lung cancer mortality was evaluated for members with more than 10 years of exposure and 20 years of latency, there was a significant SMR (2.8), and a nonsignificant exposure–response based on low and high exposure group, SMR (2.3, 3.3, respectively). Smoking was not accounted for, and only 17 cases were analyzed in total. When more than 20 years of exposure and more than 20 years of latency was applied for our data (Table 6), no consistent exposure–response could be determined, and applying cumulative cobalt exposure estimates for blue-collar workers and internal comparison showed similar results (Tables 7 and 8).

A French cohort of 709 hardmetal workers employed between 1956 and 1989 was analyzed for mortality and exposure–response patterns.¹¹ Exposure categories 1 to 4 were defined as range of cobalt air concentrations, where 1 was considered nonexposed, 2 less than 10 to 14 $\mu\text{g}/\text{m}^3$, 3 15 to 49 $\mu\text{g}/\text{m}^3$, and 4 more than 50 $\mu\text{g}/\text{m}^3$. The high exposed group (4), showed a significant SMR of 5.03, but including smoking habits, the risks among the current smokers, increased the SMRs to 9.2 and 15 for the medium and high exposed group, respectively, compared with an SMR of 7.2 for the total group of smokers. Moreover, increased mortality (SMR >1) was found for all causes, malignant neoplasms, accidents, violence, and suicide for the high exposure group. Analyses of duration of employment and latency showed no exposure–response trends. Given the smoking data for the cohort, the author concluded that smoking alone did not cause the increased risk of lung cancer, and that cobalt could be responsible for part of the enhanced risk. Our findings, which did not identify any exposure–response for internal comparison, may reflect the decreased exposure levels in our study, which included the period from 1990 onwards. It should be noted that our high exposure group, more than 0.4 mg/m³.year, reflects a 40-year exposure to 0.010 mg/m³ of cobalt, to be comparable with exposure group 2 of the French study.

In another French multicenter study, a cohort was formed from 10 different plants, with an inclusion criteria more than 3 months exposure and a mortality follow-up from 1968 to 1991.¹³ The cohort included 7459 men and women. The overall mortality for both sexes was lower than expected (SMR 0.93), and there was a borderline statistically significant excess risk of lung cancer (SMR 1.3). An increasing trend for the SMR was determined

by increased duration of exposure. The overall analysis in the case–control study showed an excess risk (OR 1.93, statistically significant). The analysis, which compared workers before and after sintering, showed nonsignificant ORs more than 1, significant trends for duration of exposure, and a significantly elevated OR (4.1, 2.73) for the high cumulative exposures. However, when adjusting for smoking, smokers (OR 3.62) showed a significantly increased risk, and workers who had never smoked (OR 1.21) showed nonsignificant risk. The high-dose group in the analysis consisted of more than 164 or more than 299 level.months; according to the given job exposure levels in the study, it would, for an example, correspond to 40 months (3.3 years) at level 4, 0.06 mg/m³, that is, 0.20 mg/m³.years. These exposure levels are in the same order of magnitude as the high exposure group in our study. The findings in the French case–control study implicate dose levels about 0.2 mg/mg/m³. years as potentially generate an increased risk of lung cancer.

Another cohort study from a French plant producing hardmetal and other cobalt products included 2860 workers.¹² The company started in 1940, and the follow-up period was 1968 to 1992. The exposure assessment was based on a 1 to 9 exposure level scale, including frequency of exposure. The mortality pattern showed no excess SMRs for all causes, the circulatory system, the respiratory system, and all cancers, except for lung cancer in men. Smoking data were retrieved from colleagues. In the hardmetal production before sintering, a significant SMR of 2.42 was determined for lung cancer. Maintenance work also showed a small increase for SMR. An analysis based on exposure scores and weighted and unweighted cumulative exposures showed significant SMRs (2.36, 2.06) for both the high exposure groups, which had been adjusted for smoking. However, no quantitative data are provided for the different exposure groups. The follow-up period of this study deviates from ours, reflecting different exposure periods.

CONCLUSION

The lung cancer incidence showed no correlation to cobalt exposure based on internal comparison. The increased SIR for all workers might be associated with other factors. There was a decreased risk for skin cancer. Increased lip cancer incidence found at one of the production plants might be related to diagnostic intensity.

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REFERENCES

- Sadik M. *An Introduction to Cutting Tools Materials and Application*. Sandviken, Sweden: Sandvik Coromant; ISBN 978-91-637-4920-9, 2nd ed. 2015.
- Balmes JR. Respiratory effects of hardmetal dust exposure. *Occup Med*. 1987;2:327–344.
- Shirakawa T, Kusaka Y, Fujimura N, et al. Occupational asthma from cobalt sensitivity in workers exposed to hardmetal dust. *Chest*. 1989;95:29–37.
- Kusaka Y, Nakano Y, Shirakawa T, Morimoto K. Lymphocyte transformation with cobalt in hardmetal asthma. *Ind Health*. 1989;27:155–163.
- Nemery B, Verbeke EK, Demedts M. Rapidly fatal progression of cobalt lung in a diamond polisher. *Am Rev Respir Dis*. 1990;141:1373–1378.
- Rehfishch P, Anderson M, Berg P, et al. Lung function and respiratory symptoms in hardmetal workers exposed to cobalt. *J Occup Environ Med*. 2012;54:409–413.
- Nakamura Y, Nishizaka Y, Ariyasu R, et al. Hardmetal lung disease diagnosed on a transbronchial lung biopsy following recurrent contact dermatitis. *Intern Med*. 2014;53:139–143.
- Barborik M, Dusek J. Cardiomyopathy accompanying industrial cobalt exposure. *Br Heart J*. 1972;34:113–116.
- Kennedy A, Dornan JD, King R. Fatal myocardial disease associated with industrial exposure to cobalt. *Lancet*. 1981;1:412–414.
- Hogstedt C, Alexandersson R. *Mortality for Hardmetal Workers (In Swedish)*. Solna, Sweden: National Institute of Occupational Health; 1990. ISBN 91 7045 0722.
- Lasfargues G, Wild P, Moulin JJ, et al. Lung cancer mortality in a French cohort of hardmetal workers. *Am J Ind Med*. 1994;26:585–595.
- Wild P, Perdrix A, Romazini S, Moulin JJ, Pellet F. Lung cancer mortality in a site producing hardmetals. *Occup Environ Med*. 2000;57:568–573.
- Moulin JJ, Wild P, Romazini S, et al. Lung cancer risk in hardmetal workers. *Am J Epidemiol*. 1998;148:241–248.
- International Agency for Research on Cancer (IARC). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 68. Cobalt in Hard Metals and Cobalt Sulfate, Gallium Arsenide, Indium Phosphide and Vanadium Pentoxide. Lyon, France: IARC Press; 2006.
- ECHA 2016. European Chemicals Agency, Substance Information, Cobalt. Available at: <http://echa.europa.eu/substance-information/-/substanceinfo/100.028.325>. Accessed October 1, 2017.
- CoRC 2013. Available at: <http://www.thecdi.com/cdi/images/documents/One-page%20statement%20Industry%20Actions%20for%20Responsible%20Assessmt%20class%20of%20Co%20compounds.pdf>. Accessed October 1, 2017.
- International Agency for Research on Cancer (IARC). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 49. Chromium, Nickel and Welding. Lyon, France: IARC Press; 1990.
- Nederlandse Vereniging voor Arbeidshygiene. Testing Compliance with Occupational Exposure Limits for Airborne Substances. Derby, UK: British Occupational Hygiene Society; September 2011.
- National Institute of Occupational Health (NIOSH). Particulates, not otherwise regulated. Method No. 0600. NIOSH Manual of Analytical Methods, 4th ed. DHHS (NIOSH) Pub. No. 94-113. Cincinnati, OH: National Institute for Occupational Safety and Health; 1994.
- Health and Safety Executive (HSE). MDHDS: General Methods for Sampling and Gravimetric Analysis of Inhalable and Respirable Dust. Report no 14/3. Suffolk, UK: Health & Safety Executive; February 2000.
- National Institute of Occupational Health (NIOSH). Cobalt and compounds by atomic absorption, flame, modified graphite furnace. Method No. 7027. NIOSH Manual of Analytical Methods, 4th ed. DHHS (NIOSH) Pub. No. 94-113. Cincinnati, OH: National Institute for Occupational Safety and Health; 1994.
- National Institute of Working Life (NIWL). X-ray fluorescence. Analysis of airborne particles (In Swedish, English summary). Lundgren L, Skare L, Persson A, Krantz S. Work Environment Health 17. Stockholm, Sweden: National Institute of Working Life; 1989.
- National Institute of Occupational Health (NIOSH). Manual of analytical methods method 7300. Elements by ICPMS. In: NIOSH Manual of Analytical Methods, 4th ed, DHHS (NIOSH) Pub. No 94-113. Cincinnati, OH: NIOSH; 1994. Modified.
- SWEA. *Occupational Exposure Limit Values (AFS 2015: 7)*. Solna, Sweden: Swedish Work Environment Authority; 2015 (In Swedish). ISBN 978-91-7930-628-1.
- Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekborn A. The Swedish personal identity number: possibilities and pitfalls in health care and medical research. *Eur J Epidemiol*. 2009;24:659–667.
- Checkoway H. Methods of treatment of exposure data in occupational epidemiology. *Med Lav*. 1986;77:48–73.
- Checkoway H, Dement JM, Fowler DP, Harris Jr RL, Lamm SH, Smith TJ. Industrial hygiene involvement in occupational epidemiology. *Am Ind Hyg Assoc J*. 1987;48:515–523.
- Kriebel D, Checkoway H, Pearce N. Exposure and dose modelling in occupational epidemiology. *Occup Environ Med*. 2007;64:492–498.
- Westberg HB, Bellander T. Epidemiological adaptation of quartz exposure modeling in Swedish aluminum foundries: nested case-control study on lung cancer. *Appl Occup Environ Hyg*. 2003;18:1006–1013.
- Symanski E, Kupper L, Hertz-Picotte I, Rappaport S. Comprehensive evaluation of long term trends in occupational exposure: part 2. Predictive models for declining exposures. *Occup Environ Med*. 1998;55:310–316.
- Andersson L, Burdorf A, Bryngelsson IIB, Westberg H. Estimating trends in quartz exposure in Swedish iron foundries-predicting past and present exposures. *Ann Occup Hyg*. 2012;56:362–372.
- International Agency for Research on Cancer (IARC). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 83. Tobacco Smoke and Involuntary Smoking. Lyon, France: IARC Press; 2004.